Nutritional Neurosciences

Nasrollah Moradikor
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Medicinal Mushrooms

An Emerging Superfood for Brain Health

Springer

Nutritional Neurosciences

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An Emerging Superfood for Brain Health

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Preface

In recent years, as we face an aging population and rising rates of neurodegenerative and mental health disorders, the need for sustainable, safe, and effective brain-supportive interventions has never been greater. Medicinal mushrooms offer a promising, largely untapped frontier in the landscape of cognitive wellness and neurotherapeutics. These ancient fungi, long used in traditional medicine systems, are now gaining recognition in modern neuroscience and nutritional therapy for their multifaceted benefits on the brain and nervous system. This book, *Medicinal Mushrooms: The Emerging Superfood for Brain Health*, explores the profound impact that edible and medicinal mushrooms can have on cognitive function, mental well-being, and the prevention of neurodegenerative disorders. This emerging complementary or alternative pharmacotherapy approaches are increasingly recognized for their efficacy to support medical care and ameliorate disease progression. One of these is the exploration of medicinal mushrooms due to their potent bioactive compounds, antioxidant properties, and potential neuroregenerative effects make them neuroprotective agents that has garnered significant interest among clinicians and researchers globally. This book chapter bridges the gap between conventional pharmacotherapy and integrative neuro-nutritional strategies, which is linked to the growing scientific evidences surrounding medicinal mushrooms. In response to the increasing burden of neurological disorders and neurodegenerative diseases, there has been a renewed hope through functional foods with promising therapeutic properties. Chapter 1 explores the cultural significance of medicinal mushrooms in diverse places across the globe and discusses scientific-based evidences of fungi species like *Hericium erinaceus* (Lion's Mane), *Ganoderma lucidum* (Reishi), and *Cordyceps sinensis* demonstrating neuroprotective, anti-inflammatory, and cognitive-enhancing potentials. Chapter 2 explains the phytochemicals in edible mushrooms such as polysaccharides, ergothioneine, triterpenoids, hericenones, cordycepin, ergosterol, and vitamins. It also describes the methods of phytochemical extraction to maximize yield and preserve bioactivity in addition to best methods to optimize their delivery across the blood-brain barrier as dietary interventions and novel therapeutics in targeted neurodegenerative disease and cognitive impairment. Chapter 3 sheds light on the best medicinal mushrooms to optimize brain health based on the emerging evidences demonstrating their significant neuroprotective, cognitive-enhancing, and adaptogenic abilities in preclinical studies, addressing neurodegenerative conditions such as Alzheimer's and Parkinson's

diseases. Chapter 4 explores medicinal mushrooms with memory and cognitive--enhancing potentials; the species of fungi include *Ganoderma lucidum* (Reishi), *Hericium erinaceus* (Lion's Mane), and *Cordyceps*. This chapter documents preclinical reports that explains their role on memory, neuroplasticity, and cognitive functions through the brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) mechanisms crucial for neuronal growth, survival, and synaptic plasticity. Chapter 5 is directed to explore the molecular basis and mechanisms through which medicinal mushrooms exhibit their immunomodulatory, antioxidant, and neuroprotective roles. This chapter highlights various phytochemicals in medicinal mushroom and through scientific based evidences describes how them demonstrates their neuroprotective roles through metal ion chelation, upregulating the Nrf2/ARE pathway, GluN1/GluN3A and GluN1/GluN3B receptors, regulating of cytokines like IL-10 and TGF-β, PI3K/Akt pathway crucial in modulating neuronal growth, proliferation and NF-κB pathway to mention a few. Chapter 6 explains how medicinal mushrooms such as *Hericium erinaceus*, *Cordyceps militaris*, and *Ganoderma lucidum* demonstrate mood-regulating properties in preclinical studies directed toward mood disorders such as depression and anxiety by modulating serotonin receptors, anti-inflammation, neuroplasticity, and gut–brain axis regulation. Chapter 7 explores important bioactive compounds in mushrooms, such as polysaccharides, peptides, and phenolic compounds, and how they mitigate signaling cascades such as the Nrf2/ARE and NF-κB pathways in neuroinflammation and neurodegeneration using recently documented preclinical and clinical evidences. Chapter 8 discussed therapeutic roles of medicinal mushroom in Alzheimer's disease through NGF stimulation, stress reduction, neurotransmitter modulation, and antioxidant and anti-inflammatory activity. Parkinson's disease, which is a neurodegenerative disorder that causes both motor and non-motor symptoms, is a global burden with poor therapeutic prognosis. Chapter 9 discussed preclinical trial evidences of medicinal mushrooms to control anti-apoptotic signaling and support dopaminergic neurotransmission, in Parkinson's disease management. Nutrition is a basic determinant of brain health and can also be a modifiable risk factor associated with progression of dementia. In this book, Chapter 10 explains mushrooms as an effective nutritional intervention for dementia management. Our scientific review of the role of medical mushrooms as nutrition intervention revealed that mushrooms have psilocybin, which is significant in neurocognition and neuroplasticity. For instance, we discussed on a recent report on how *Hericium erinaceus* averts cognitive decline, supports neuroplasticity, and improves neurite growth factor for synaptic integrity. It is important to say that the human brain undergoes complex anatomical and physiological changes in human, which includes period of early brain development, postnatal, and the aging brain. In this final chapter we discussed medicinal mushroom as a superfoods and cognitive booster in human lifespan attributed to its phytochemicals that promote brain development and delay age-related neurodegeneration. We laid emphasis on the various medicinal mushrooms and their influence on brain development and aging through empirical evidences in preclinical studies reporting role in adenosine A2 receptor, microglial activation, and neuroinflammatory markers like NF-κB and NLRP3 inflammasome to mention a few, ultimately

demonstrating medicinal mushrooms as promising natural agents in promoting cognitive vitality from infancy through old age. This book integrates both basic science and translational empirical data to shed light on the complementary role of medicinal mushrooms in Parkinson's disease management, in developing and aging brain therapy. It is our hope that this work will contribute to scientific knowledge in pharmacotherapy intervention in neurodegeneration and inspire clinicians, researchers, and students to consider the valuable intersection of nutrition, pharmacology, and neuroscience in shaping the future of integrative or complementary neurotherapeutics in neurodegenerative disorders.

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An Overview of the Nutritional and Potential Health Benefits of Medicinal Mushrooms

1

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Abstract

For centuries, medicinal mushrooms have played a vital role in traditional healing systems across the globe, prized for their wide-ranging therapeutic properties, particularly their potential to support brain health. In response to the escalating global burden of mental health disorders and neurodegenerative diseases, there has been a renewed focus on natural, functional foods as promising preventive and therapeutic agents. This chapter explores medicinal mushrooms' historical and cultural significance in diverse regions—including Asia, Europe, Africa, the Americas, and Oceania—and connects these long-standing practices with modern consumption patterns. The global medicinal mushroom market is expanding significantly, propelled by rising consumer interest in natural cognitive enhancers and stress-relief agents. Today, these fungi are available in a variety of formats such as teas, tinctures, powders, and functional food products, with species like *Hericium erinaceus* (Lion's Mane), *Ganoderma lucidum* (Reishi), and *Cordyceps sinensis* emerging as key players in cognitive wellness. Growing scientific research continues to substantiate traditional applications by isolating bioactive constituents—polysaccharides, triterpenoids, and

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hericenones—demonstrating neuroprotective, anti-inflammatory, and cognitive-enhancing properties. Additionally, current trends reflect the integration of medicinal mushrooms into contemporary dietary lifestyles, including plant-based, ketogenic, and paleo regimens, as well as their rising prominence in the brain health and nootropic markets. Future directions emphasize the need for rigorous clinical trials, improved bioavailability of active constituents, standardized regulatory frameworks, and the development of personalized interventions. As the intersection between ethnomycology and modern neuroscience deepens, medicinal mushrooms are gaining recognition as valuable tools in the global pursuit of enhanced cognitive resilience and emotional well-being.

Keywords

Medicinal mushrooms · Neuroprotection · Cognitive health · *Hericium erinaceus* · Functional foods · Traditional medicine · Brain aging · Neuroinflammation

1.1 Introduction

The patterns and rate of global population aging vary considerably by region, with high- and middle-income nations presently undergoing the most pronounced demographic transitions. Increased life expectancy, declining fertility rates, and a complex interplay of biological, environmental, and sociocultural changes largely drive this phenomenon. With the progressive aging of the global population, the incidence of neurodegenerative disorders is increasing markedly. It is estimated that around 14% of the world's population suffers from some form of mental disorder. Moreover, approximately 15% of children and adolescents are affected by mental health challenges, often stemming from physical, emotional, or social stressors such as poverty, abuse, or exposure to violence (Reynolds et al. 2022). These disorders significantly contribute to the global disease burden, affecting individual and community health by impairing cognitive and motor functions. The consequences include a significant decline in quality of life, ongoing stigma and discrimination, and an increasing burden on healthcare organizations globally (Guo et al. 2022; Lim et al. 2024). To address obstacles and promote the incorporation of mental health into mainstream healthcare, the WHO launched the Mental Health Action Plan 2013–2020. Acknowledging the persistent need for holistic mental health approaches, the initiative was prolonged to 2030 during the 72nd World Health Assembly in May 2019, aligning it with the overarching goals of the 2030 Agenda for Sustainable Development (Singh 2021). More than 600 distinct disorders affecting the nervous system have been identified, encompassing over 200 recognized categories of mental illnesses (Dumurgier and Tzourio 2020). The definition of mental disorders continues to evolve through successive revisions. A mental disorder is characterized by significant clinical impairment in emotional regulation, cognition, mood, behavior, and functionality, often causing distress in critical areas of

daily life. These conditions may be acute or chronic, persisting for short durations or throughout a person's life (Stein et al. 2021).

Mental health disorders comprise a broad range of conditions, including emotional regulation issues such as bipolar disorder, various anxiety disorders, personality disorders, and eating disorders like binge eating, bulimia, and anorexia. Additionally, significant conditions are schizophrenia, post-traumatic stress disorder, and substance use disorders (Burback et al. 2024). The International Classification of Diseases (ICD-11), published by the WHO in 2022, acts as the worldwide benchmark for multilingual and digital documentation of health conditions, featuring more than 17,000 distinct codes and 120,000 codable terms, inclusive of entries related to traditional medicine, and presently translates over 1.6 million terms (WHO ICD-11 2022). Mental health disorders are on the rise globally. As of 2024, one in every eight individuals—approximately 970 million people—live with a mental disorder. In the European Union alone, 84 million people (roughly one in six) are affected by a form of cerebral disability (Amand-Eeckhout 2024). Emotional control, behavior, or cognition disturbances linked to anxiety and depressive disorders are the most common mental health conditions. Worldwide, depression affects approximately 280 million individuals, while anxiety disorders impact more than 300 million people (Institute of Health Metrics and Evaluation Global Health Data Exchange 2025; Moitra et al. 2022).

Given the multifactorial nature of mental illness, a wide array of risk factors can contribute to its onset. Therefore, it is essential to identify both risk and protective factors as early as possible across developmental stages to enable timely and effective interventions (Carbone 2020; Colizzi et al. 2020). Although prevention has long been a foundational concept in medical practice, its widespread acceptance in mental health has only emerged more recently (Fusar-Poli et al. 2021). Preventive strategies for mental disorders must be grounded in a rigorous and ethical examination of risk factors, since not all available data may justify the development of specific preventive interventions (Haggerty and Mrazek 1994). Mental illnesses such as anxiety, mania, and depression significantly contribute to global disability, causing considerable social, economic, and public health issues around the world (Wu et al. 2023).

In this context, food and nutrition, particularly mushroom-based nutrition, are gaining recognition as important contributors to the prevention and management of neurological disorders (Bell and Fernandes 2023). Nutraceutical strategies, incorporated into personalized dietary interventions utilizing bioactive compounds, are increasingly recognized as powerful adjuncts for neural regeneration, recovery, and therapy. These approaches have shown potential in improving cognitive dysfunction linked to neurological conditions, including Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), anxiety, and depression (Ciancarelli et al. 2024; Dominguez et al. 2024; Grabska-Kobyłecka et al. 2023; Osakabe et al. 2024).

Extensive research has been conducted on various types of mushrooms (Fig. 1.1). Approximately 14,000 mushroom species have been identified. Among these, around 2000 species are safe for consumption, and nearly 650 species are recognized for their medicinal properties (Table 1.1) (Thatoi and Singdevsachan 2014).

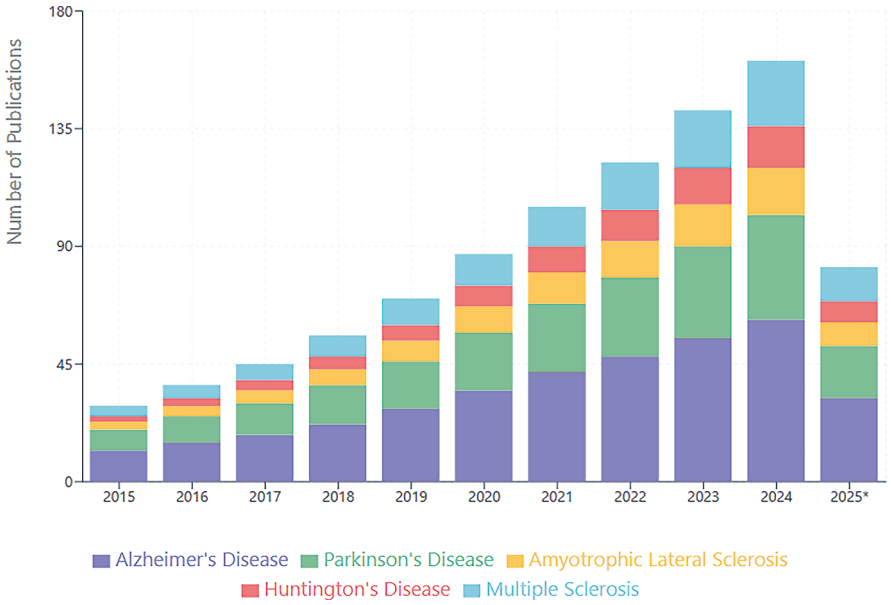

Fig. 1.1 This stacked bar chart illustrates the temporal distribution of research publications investigating mushroom therapeutic potential across five major neurodegenerative diseases from 2015 to 2025, revealing a consistent upward trend with peak activity in 2023–2024. Alzheimer's disease research dominates the field, accounting for approximately 40% of all publications, followed by Parkinson's disease studies, reflecting the established neuroprotective mechanisms and clinical accessibility of these conditions for mushroom-based interventions. The research primarily focuses on *Hericium erinaceus* (Lion's Mane) for its nerve growth factor-stimulating properties, *Ganoderma lucidum* (Reishi) for its anti-inflammatory triterpenes, and *Cordyceps* species for their neuroprotective metabolites. The underlying mechanisms investigated encompass direct neuroprotection through antioxidant activity and mitochondrial support, neuroinflammation reduction via microglial modulation and cytokine regulation, and neurogenesis promotion through enhanced brain-derived neurotrophic factor expression and synaptic plasticity, collectively demonstrating the multifaceted therapeutic potential of fungal bioactive compounds in addressing the complex pathophysiology of neurodegenerative disorders

Traditional medicine systems have long utilized species such as *Auricularia*, *Flammulina*, *Ganoderma*, *Grifola*, *Lentinula*, *Trametes*, and *Tremella* for their health benefits (SJAMB Wasser 2002). Many of these mushrooms have demonstrated a wide range of bioactivities, including antibacterial, antifungal, antiviral, antioxidant, anti-inflammatory, cytotoxic, antiproliferative, antitumor, hepatoprotective, hypocholesterolemic, antidiabetic, anticoagulant, and anti-HIV effects (Hassan et al. 2015; Phan et al. 2015; Wasser 2014).

Clinically important species such as *Agaricus bisporus*, *Agaricus blazei*, *Agaricus sylvaticus*, *G. lucidum*, *Lentinula edodes*, *Grifola frondosa*, *Hericium erinaceus*, and *Pleurotus ostreatus* are known for their rich profiles of bioactive compounds. These include polysaccharides, proteins, fats, alkaloids, glycosides, phenolics, carotenoids, organic acids, terpenes, and notably, triterpenes. Several

Table 1.1 Bioactive compounds in medicinal mushrooms and their brain health pathways

Mushroom species	Bioactive compound	Chemical class	Brain health category	Cellular mechanism
Lion's Mane (*Hericium erinaceus*)	Hericenones A-H	Diterpenoids	Neuroprotection & cognition enhancement	Stimulates NGF synthesis
	Erinacines A-K	Cyathane diterpenoids		Crosses the blood–brain barrier, enhances NGF production
Reishi (*Ganoderma lucidum*)	Ganoderic acids A-Z	Lanostane triterpenoids	Neuroprotection and anti-inflammatory	Inhibits neuroinflammation, reduces oxidative stress
	Ganoderma polysaccharides	β-glucans		Modulates immune response, antioxidant activity
Cordyceps (*Cordyceps sinensis*)	Cordycepin	Nucleoside analog	Neuroprotection and cognition enhancement	Adenosine receptor modulation, neuroprotective effects
	Cordyceps polysaccharides	β-glucans	Anti-inflammatory and neuroprotection	Anti-inflammatory, antioxidant properties
Shiitake (*Lentinula edodes*)	Lentinan	β-1,3-glucan	Anti-inflammatory and neuroprotection	Immune system modulation, anti-inflammatory
	Eritadenine	Purine derivative	Neuroprotection	Improves cerebral circulation, neuroprotective
Turkey Tail (*Trametes versicolor*)	Polysaccharide-K (PSK)	Protein-bound polysaccharide	Anti-inflammatory and neuroprotection	Immune modulation, anti-inflammatory effects
	Trametes polysaccharides	β-glucans	Anti-inflammatory	Reduces neuroinflammation, antioxidant activity
Chaga (*Inonotus obliquus*)	Betulinic acid	Pentacyclic triterpenoid	Neuroprotection and anti-inflammatory	Antioxidant, anti-inflammatory, neuroprotective
	Inotodiol	Lanostane triterpenoid	Neuroprotection	Antioxidant properties, cellular protection

(continued)

Table 1.1 (continued)

Mushroom species	Bioactive compound	Chemical class	Brain health category	Cellular mechanism
Maitake (*Grifola frondosa*)	Grifolan	β-glucan	Anti-inflammatory and neuroprotection	Immune modulation, anti-inflammatory
	D-fraction	Protein-bound β-glucan	Anti-inflammatory	Anti-inflammatory, immune balancing
Oyster Mushroom (*Pleurotus ostreatus*)	Pleuran	β-1,3/1,6-glucan	Anti-inflammatory and neuroprotection	Immune modulation, antioxidant effects
	Lovastatin	Statin compound	Neuroprotection	Cholesterol regulation, vascular protection
Enoki (*Flammulina velutipes*)	Flammulin	Protein	Neuroprotection	Antioxidant, cellular protective effects
Wood Ear (*Auricularia auricula*)	Auricularia polysaccharides	Heteropolysaccharides	Anti-inflammatory and neuroprotection	Anti-inflammatory, anticoagulant properties

well-studied compounds from these mushrooms—such as calcaelin, ganoderic acid, grifron, hispolon, illudin S, lentinan, schizophyllan, and psilocybin—exhibit significant therapeutic potential, particularly in neurological and psychiatric applications.

This chapter explores the global consumption patterns of medicinal mushrooms, with a focus on their role in supporting brain function. It integrates historical usage, contemporary trends, and emerging research to provide a comprehensive overview of how these natural agents may contribute to cognitive wellness and the prevention of neurological disorders.

1.2 Medicinal Mushrooms and Their Bioactive Compounds in Brain Health

(a) *Maitake (Grifola frondosa)*

Maitake is a nutritional mushroom rich in protein, carbohydrates, fiber, vitamin D, and essential minerals. It contains over 47 bioactive compounds known for their anti-inflammatory, antitumor, and antiviral effects. The specific compounds extracted and their pharmacological effects can vary significantly depending on the extraction method used (Wu et al. 2021).

Maitake also exhibits notable antioxidant activity. In a study using an aged rat model, maitake supplementation was associated with improvements in memory and learning (Chen et al. 2017). Brain tissue analysis revealed reduced neuronal shrinkage and higher cell density in the hippocampus, the brain region responsible for memory formation. Additionally, maitake treatment reduced the number of damaged mitochondria and oxidative stress markers that typically increase with age. These findings suggest that maitake's cognitive benefits may stem from its antioxidant properties, potentially offering protection against age-related neurodegeneration (Chen et al. 2017).

(b) *Cordyceps (Cordyceps sinensis or militaris)*

Cordyceps have also demonstrated antioxidant properties that are relevant to brain health. Veena et al. studied the effect of *cordyceps* in a rat model of chemotherapy-induced cognitive dysfunction and observed increased antioxidant enzyme activity and cellular energy levels following treatment (Veena et al. 2020). Similar cognitive improvements were noted in another study involving rats with learning and memory impairments, where treatment with *cordyceps* led to elevated superoxide dismutase activity, a key enzyme that mitigates oxidative stress (Yuan et al. 2018).

Cordymin, a bioactive compound isolated from *cordyceps*, showed neuroprotective effects in an animal stroke model. Treated animals displayed improved motor function, reduced oxidative stress, and decreased inflammation. Overall, rats receiving Cordymin experienced less neuronal death compared to untreated controls (Wang et al. 2012). Pal et al. performed in vitro studies using mouse hippocampal neurons and found that *cordyceps* conferred protection against hypoxia-induced

oxidative stress by decreasing free radical generation and enhancing antioxidant defense systems. Additionally, it reduced the secretion of inflammatory cytokines in the hippocampal cells (Pal et al. 2015).

Other significant effects of *cordyceps* treatment include increased levels of brain-derived neurotrophic factor (BDNF), results in boosting neuronal survival and plasticity, as well as a reduction in neuroinflammation in a mouse model of AD (He et al. 2021). In traditional Chinese medicine, *cordyceps* has been used to manage conditions such as epilepsy and anxiety. Lin et al. reported antidepressant-like effects in rats, demonstrated by decreased inactivity and increased sucrose consumption, indicative of improved mood (Lin et al. 2021). These behavioral improvements were accompanied by normalized serotonin turnover in the frontal cortex. Notably, low-dose *cordyceps* (125 mg/kg) produced effects similar to the antidepressant fluoxetine (Prozac), suggesting its potential as a natural mood enhancer (Lin et al. 2021)

(c) *Reishi (Ganoderma lucidum)*

Reishi is another mushroom with neuroprotective potential, particularly against age-related cognitive decline. In a murine model of AD, reishi extract improved memory performance and preserved hippocampal neuron structure and function (Rahman et al. 2020). A 2013 study on seizure-prone rats found that reishi helped prevent convulsions, reduced inflammatory molecules, and minimized neurodegeneration in the hippocampus (Tello et al. 2013). Reishi also countered the neurotoxic effects of alcohol consumption, which can result in long-term cognitive deficits (Shevelev et al. 2015). Treated rats showed improved brain energy metabolism, normalized neurotransmitter levels, and reduced liver cell proliferation associated with alcohol intake, indicating a neuroprotective role for reishi.

(d) *Turkey Tail (Trametes versicolor)*

Turkey tail contains several beneficial bioactive compounds, including vitamin B3 (nicotinic acid and nicotinamide), essential fatty acids (linoleic, oleic, palmitic, stearic, and linolenic), and amino acids (leucine, isoleucine, methionine, tyrosine, glutamine, and asparagine) (Kıvrak et al. 2020). Vitamin B3 is essential for cellular energy metabolism through its conversion to NAD, a coenzyme vital for numerous enzymatic reactions. Additionally, amino and fatty acids support brain function and facilitate cellular communication. For instance, the amino acid tyrosine serves as a precursor for critical neurotransmitters like epinephrine, norepinephrine, and dopamine, which play essential roles in managing mood and responding to stress.

(e) *Lion's Mane (Hericium erinaceus)*

Lion's Mane is among the most widely studied and commonly used medicinal mushrooms for brain health. It has been investigated for its potential benefits in cognitive impairment, stroke (Lee et al. 2014), PD (Kuo et al. 2016), AD (Tsai-Teng et al. 2016), and more recently, depression (Chong et al. 2020). Its neuroprotective properties are primarily attributed to its active compounds—hericenones and erinacines—which have been shown to promote the synthesis of NGF, essential for neuron development and survival.

In a preclinical study, the compound amycenone, extracted from Lion's Mane, was administered to mice with lipopolysaccharide-induced inflammation and depressive symptoms. Treatment with amycenone reduced immobility in behavioral tests and modulated inflammatory cytokine levels, suggesting decreased neuroinflammation (Yao et al. 2015). A 2018 study found that ethanolic extracts of Lion's Mane had a significant impact on reducing anxiety and depressive behaviors in rats. Treated rats exhibited greater exploratory behavior, and further analysis revealed increased hippocampal neurogenesis and neuronal density (Ryu et al. 2018).

Human clinical trials also support Lion's Mane's cognitive and mood-enhancing properties. In menopausal women, taking Lion's Mane supplements has been shown to alleviate symptoms of anxiety and depression. Another trial involving 77 overweight and obese individuals found improvements in binge eating, sleep quality, and mood following 8 weeks of supplementation. These effects were accompanied by increased levels of BDNF, which supports neuroplasticity and cell survival (Luisella Vigna et al. 2019). However, larger-scale trials are necessary to confirm the efficacy and long-term effects of Lion's Mane. One clinical trial involving Japanese adults demonstrated significant enhancement in cognitive function after 16 weeks of consuming Lion's Mane. However, the benefits declined after discontinuation, suggesting that sustained intake may be required for continued effectiveness

(f) *Chaga (Inonotus obliquus)*

Chaga is rich in polysaccharides, particularly beta-glucans, which contribute to its medicinal properties. In studies involving Alzheimer's disease models, chaga treatment improved brain cell survival, reduced pro-inflammatory markers, and decreased amyloid-beta plaque accumulation—a key feature of Alzheimer's pathology (Xin et al. 2021; Han et al. 2019). Chaga lowered inflammation and oxidative stress levels in aged rats while preserving cognitive performance. Chaga's therapeutic actions appear to be mediated by activation of the Nrf2 pathway, a key regulator of cellular antioxidant responses that increases detoxification protein production.

In addition to its cognitive benefits, chaga may also help combat fatigue. In a forced swim test, mice treated with chaga swam longer than controls, suggesting reduced physical fatigue (Zhang et al. 2020). Elevated brain serotonin levels, which typically rise with physical exertion and are linked to fatigue, were lower in chaga-treated mice. This implies that chaga may enhance energy metabolism and delay mental fatigue, although more research is needed to understand the mechanisms involved fully.

1.3 Traditional and Cultural Use of Medicinal Mushrooms Across the Globe

Medicinal mushrooms have played a vital role in traditional medicine across continents for centuries. In Asia, particularly China, Japan, and Korea, species like *G. lucidum* (Reishi), *H. erinaceus* (Lion's Mane), and *Cordyceps sinensis* are deeply

valued. Reishi, known as the "mushroom of immortality," was historically used by Chinese emperors to promote longevity and spiritual clarity (Wasser 2002). Buddhist monks consumed lion's Mane to enhance focus, a practice supported today by evidence of its NGF-stimulating and neuroprotective properties (Contato and Conte-Junior 2025a). In Korea, *Cordyceps* has been used traditionally to increase stamina and vitality (Shweta et al. 2023).

In Russia and Eastern Europe, *Inonotus obliquus* (Chaga) has long been brewed into teas for immune health. Similarly, Scandinavian cultures utilized fungi like *Fomitopsis officinalis* for treating respiratory ailments and inflammation (Lindequist et al. 2005).

In the Americas, indigenous Mesoamerican peoples used psychoactive mushrooms in spiritual rituals. While distinct from non-hallucinogenic medicinal species, this use reflects the cultural importance of fungi. In modern North America, growing interest in wellness and nootropics has led to the widespread adoption of mushroom supplements, particularly Lion's Mane, Chaga, and Turkey Tail (*Trametes versicolor*), prized for cognitive and immune support (Ratto et al. 2019).

In Africa and Oceania, traditional documentation is sparse, yet interest is expanding. Australia and New Zealand, in particular, are integrating mushrooms into health practices, driven by their antioxidant and anti-inflammatory potential (Mori et al. 2009).

Modern research has validated many of these historical uses, identifying bioactive compounds such as polysaccharides, triterpenes, and hericenones that exert neuroprotective, immunomodulatory, and anti-inflammatory effects (Fig. 1.2) (Long et al. 2021; Szućko-Kociuba et al. 2023). These findings bridge ancient traditions with modern science, highlighting the global value of medicinal mushrooms.

1.4 Contemporary Consumption Patterns

The global consumption of medicinal mushrooms has surged in recent years, fueled by growing interest in natural remedies and increasing scientific support for their health benefits. Valued at approximately USD 67.69 billion in 2024, the medicinal mushroom market is anticipated to achieve a value of USD 182.34 billion by the year 2033, with a projected compound annual growth rate (CAGR) of 11.64% (Business Research Insights 2025). This growth is driven by rising demand for functional foods, preventive healthcare, and plant-based diets. While Asia-Pacific remains the dominant market due to its traditional roots, North America and Europe are quickly expanding, supported by improved product availability through online platforms, supermarkets, and health stores (Coherent Market Insights 2025).

Modern consumption has evolved beyond traditional preparations, with powders, capsules, and tinctures becoming widely popular. Dual-extracted powders—rich in polysaccharides like beta-glucans and triterpenoids—are frequently added to smoothies and meals. Capsules offer convenient dosing, while tinctures ensure rapid absorption. There's also growing innovation in functional foods and

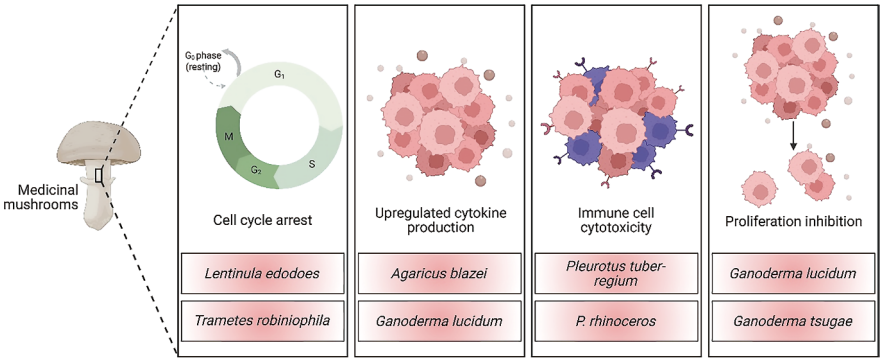

Fig. 1.2 This figure illustrates the diverse anticancer mechanisms exhibited by various medicinal mushroom species and their associated cellular targets. The diagram presents a systematic overview of four distinct pathways through which fungal bioactive compounds exert their therapeutic effects against cancer cells. The left panel depicts the cell cycle arrest mechanism, showing the classical cell cycle phases (G_0/G_1, S, G_2, and M phases), emphasizing cell cycle checkpoint disruption. This mechanism is primarily associated with *Lentinula edodes* (shiitake mushroom) and *Trametes robiniophila* (white rot fungus), which contain polysaccharides and triterpenes that interfere with cyclin-dependent kinase activity and cell cycle progression, effectively halting malignant cell division. The second panel illustrates upregulated cytokine production, represented by clustered hexagonal cellular structures surrounded by smaller cytokine molecules. This immunomodulatory mechanism is characteristic of *Agaricus blazei* (Brazilian mushroom) and *Ganoderma lucidum* (reishi mushroom), promote the synthesis of pro-inflammatory cytokines, including interferon-γ, interleukin-1β, and tumor necrosis factor-α, enhancing the host's immune surveillance against tumor cells. The third panel demonstrates immune cell cytotoxicity, showing the interaction between immune effector cells (depicted in blue) and target cancer cells (shown in pink/red). The Y-shaped structures represent antibodies or immune recognition molecules facilitating targeted cell destruction. This mechanism is exemplified by *Pleurotus tuber-regium* (king tuber oyster mushroom) and *Pleurotus rhinoceros*, which enhance natural killer cell activity and cytotoxic T-lymphocyte function through β-glucan-mediated immune activation. The fourth panel represents proliferation inhibition, showing a transition from clustered malignant cells to dispersed, reduced cellular populations, indicated by the downward arrow. This antiproliferative effect is associated with *G. lucidum* and *G. tsugae*, which contain ganoderic acids and other triterpenes that induce apoptosis and inhibit angiogenesis, thereby limiting tumor growth and metastatic potential. The connecting dashed lines from the central "Medicinal mushrooms" label emphasize that these fungi serve as a unified source of multiple bioactive compounds capable of targeting cancer through complementary mechanisms. This approach that targets multiple pathways suggests a notable benefit compared to traditional single-pathway treatment methods, as it addresses tumor heterogeneity and reduces the likelihood of drug resistance development. (All figures have been created using BioRender.com)

beverages, such as mushroom-infused coffees, protein bars, and plant-based meat alternatives (Hazarika et al. 2025; Prasad et al. 2015).

Medicinal mushrooms are increasingly featured in the nootropic and cognitive enhancement markets. *H. erinaceus* (Lion's Mane) is especially prized for stimulating NGF, potentially improving memory, focus, and mental clarity (Contato and Conte-Junior 2025b). It is commonly paired with *G. lucidum* (Reishi), known for its

calming effects, and *Cordyceps* for energy and endurance. These natural nootropics appeal to consumers seeking safer, plant-based cognitive boosters.

Aligned with dietary trends like veganism, paleo, and keto, mushrooms offer low-calorie, nutrient-dense, and adaptogenic properties. Their umami flavor and texture also make them ideal meat alternatives, enhancing their culinary and therapeutic appeal (Hazarika et al. 2025; Losoya-Sifuentes et al. 2025).

This multifaceted integration into wellness, nutrition, and cognitive health positions medicinal mushrooms as a lasting force in the global health and food landscape.

1.5 Clinical Trials Linking Medicinal Mushrooms to Brain Health

Ganoderma lucidum has been widely used in Asia for treating various conditions, including cancer, diabetes, and neurasthenia. Among these, its effects on neurasthenia appear particularly promising. This is supported by a randomized, double-blind, placebo-controlled clinical trial conducted by Tang et al. that focused on Ganopoly®. In the study, 132 patients diagnosed with neurasthenia were randomly assigned to receive either a placebo or 1800 mg of Ganopoly® three times a day for 8 weeks. By the end of the treatment period, participants in the *G. lucidum* group reported a significantly improved sense of well-being, as measured by the Visual Analogue Scale (VAS), along with notable decreases in the Clinical Global Impression (CGI) severity scale scores and levels of fatigue.

Numerous clinical studies have highlighted the therapeutic benefits of *H. erinaceus*. For instance, a study by Mori et al. (2009) involved a double-blind, parallel-group, placebo-controlled trial with 30 participants suffering from mild cognitive impairment. These individuals were given either four tablets (each 250 mg and containing 96% mushroom powder) or a placebo, which they took three times a day for 16 weeks, followed by a 4-week observation phase. Cognitive performance was evaluated using the Revised Hasegawa Dementia Scale (HDS-R). The yamabushitake-treated group exhibited significantly higher cognitive scores at weeks 8, 12, and 16 and at the 4-week follow-up. However, scores declined significantly after discontinuing the supplement, indicating the possible need for ongoing administration. Nevertheless, the findings highlight the utility of this mushroom in managing mild cognitive impairment.

Following these positive results, Li et al. carried out a randomized, double-blind, placebo-controlled pilot study to evaluate the efficacy of *H. erinaceus* in treating early-stage AD. Participants took three capsules daily, each containing 350 mg of *H. erinaceus* mycelium, standardized to include 5 mg of erinacin A, over a 49-week period. Compared to the placebo group, those who received the mushroom supplement demonstrated significant improvements in their scores for Instrumental Activities of Daily Living, the Mini-Mental State Examination, and measures of contrast sensitivity. Additionally, while the average apparent diffusion coefficient (ADC) values in the arcuate fasciculus of the dominant hemisphere showed a significant increase in the placebo group, this change was not seen in those receiving

H. erinaceus. Importantly, the treated group exhibited a significant reduction in ADC values in the parahippocampal cingulum area, suggesting a potential neuroprotective benefit.

Nagano et al. investigated the effects of *H. erinaceus* on the autonomic nervous system and cognitive functioning through a randomized, double-blind, placebo-controlled trial aimed at assessing its influence on depression, sleep quality, menopausal symptoms, and other nonspecific complaints. The evaluations employed included the Kupperman Menopausal Index (KMI), Pittsburgh Sleep Quality Index (PSQI), Center for Epidemiologic Studies Depression Scale (CES-D), and the Indefinite Complaints Index (ICI). Thirty female participants were randomly assigned to receive either four cookies containing *H. erinaceus* powder (0.5 g per cookie) or placebo cookies daily for a duration of 1 month. The findings revealed significant improvements in CES-D and ICI scores in the treatment group after the intervention.

Additionally, the terms "insensitive" and "palpitation" from the ICI showed considerably greater reductions compared to placebo, while "concentration," "irritability," and "anxiety" tended to be lower. These findings led the authors to propose that the anxiolytic and antidepressant effects of *H. erinaceus* may operate through mechanisms distinct from its well-known NGF-enhancing activity.

A case report by Inanaga highlighted the use of *H. erinaceus* in an 86-year-old patient diagnosed with mild cognitive impairment and recurrent depressive disorder, who was also undergoing treatment with mirtazapine. After a 6-month regimen of HE extract administered as Amyloban® 3399 (Mushroom Wisdom, Inc., East Rutherford, NJ, USA; US patent pending), enhancements were observed in both cognitive function and body weight. Okamura et al. conducted a pilot study (Khatun et al. 2007) to evaluate the effects of the same supplement on sleep disorders in eight female undergraduate students. Participants took six tablets daily for 4 weeks, and assessments were conducted using the General Health Questionnaire (GHQ-28) and PSQI. Both anxiety and insomnia symptoms showed a downward trend, with corresponding reductions in PSQI scores. Notably, anxiety and insomnia symptoms exhibited a decline, correlating with reductions in PSQI scores. Following treatment, raised amounts of salivary free 3-methoxy-4-hydroxyphenylglycol (free MHPG)—a biomarker associated with chronic stress and depressive symptoms linked to sympathetic nervous system activity—were observed.

While these findings suggest that *H. erinaceus* may benefit sleep quality, mood, and overall well-being, the authors caution that the small sample size and timing of the study, just before major national examinations, limit the generalizability of the results. The participants likely did not meet the clinical severity or chronicity criteria typically required for diagnosing anxiety or mood disorders.

A more recent randomized clinical trial explored the efficacy of *H. erinaceus* in alleviating depression, anxiety, sleep disturbances, and binge eating behavior (Vigna et al. 2019). In this study, 77 overweight or obese participants diagnosed with one or more mood disorders were allocated to receive a daily regimen of three capsules of the *Hericium* dietary supplement, branded as "Mycotherapy Hericium," over a 2-month period while adhering to a caloric restriction

protocol. The formulation consisted of 80% mycelial biomass and 20% fruiting body extract. Psychological assessments were performed at three intervals: prior to treatment, during the intervention, and posttreatment. These evaluations utilized several established tests, including the Symptom Checklist-90 (SCL-90), Zung's Depression Scale, Zung's Anxiety Scale, and the Binge Eating Scale (BES). The findings indicated statistically significant enhancements in depressive symptoms, anxiety levels, and sleep quality within the treatment group relative to the control group. This indicated statistically meaningful enhancements in the domains of depression, anxiety, and sleep quality among participants in the treatment group compared to the control. Furthermore, an increase in circulating pro-BDNF levels was observed. However, it remains unclear whether pro-BDNF and mature BDNF can be reliable biomarkers of mood disorders, warranting further investigation.

1.6 Future Research Directions and Innovations

The future of medicinal mushrooms in brain health and cognitive wellness holds tremendous promise. As public interest grows and preliminary studies show encouraging results, there is a clear need for large-scale, placebo-controlled clinical trials to validate the cognitive and neuroprotective benefits of key species such as *Hericium erinaceus*, *Ganoderma lucidum*, and *Cordyceps sinensis*. Future research should prioritize the identification of the exact molecular mechanisms through which medicinal mushrooms exert their effects, with particular emphasis on key pathways such as NGF signaling, BDNF activity, neuroinflammatory responses, oxidative stress regulation, and neurotransmitter modulation. Progress in formulation science is also expected to advance this field. Novel delivery systems—such as nanoencapsulation techniques or dual-extraction processes—could significantly improve the bioavailability and therapeutic potential of bioactive compounds derived from mushrooms. Additionally, integrating genomic data and microbiome analysis may open new avenues for personalized approaches, enabling tailored mushroom-based interventions based on individual genetic profiles and gut–brain axis characteristics. From a policy perspective, developing internationally recognized standards for quality assurance, safety, and efficacy will be essential as the global market for these products continues to grow. Strengthening interdisciplinary collaboration among neuroscientists, ethnobotanists, nutritionists, and biotechnologists will further enrich our understanding of how these fungi can support cognitive function and mental health across varied populations. Collectively, these developments hold the potential to transition medicinal mushrooms from traditional remedies to evidence-based interventions that play a meaningful role in promoting brain health and preventing neurodegenerative conditions.

1.7 Conclusion

Medicinal mushrooms offer a compelling bridge between traditional healing wisdom and contemporary neuroscience. With demonstrated neuroprotective, anti-inflammatory, and cognitive-enhancing effects, species such as *H. erinaceus*, *Cordyceps*, and *Ganoderma lucidum* are emerging as valuable allies in addressing the global burden of mental and neurodegenerative disorders. Modern consumption trends and robust market expansion indicate growing public confidence and interest in medicinal mushrooms. As scientific research continues to accumulate, these fungi are poised to influence the development of future dietary approaches, therapeutic strategies, and integrative models of brain health and cognitive aging. Sustained interdisciplinary collaboration and ethical commercialization will be key to unlocking their full potential in promoting global mental well-being.

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Edible Mushrooms: Structure, Key Compounds, and Biological Effects

2

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Abstract

Edible mushrooms are becoming recognized as significant sources of neuroprotective compounds with potential application in brain health and disease prevention. This chapter examines current evidence on a wide range of edible mushrooms from commonly consumed species such as *Agaricus bisporus* and *Pleurotus ostreatus*, to less commonly consumed species such as *Cordyceps militaris* and *Psilocybe cubensis*. Fungal-derived metabolites of interest include polysaccharides (such as β-glucans), ergothioneine, triterpenoids, erinacines/hericenones, cordycepin, ergosterol, and vitamins (B-vitamins, vitamin D). Extraction strategies, ranging from conventional hot water and acid-base protocols to advanced techniques such as response surface methodology (RSM), ultrasound- and microwave-assisted, subcritical water, and enzyme-assisted extraction, are techniques used for maximizing yield and preserving bioactivity. Delivery across the blood–brain barrier can be optimized by using nanoparticle encapsulation (e.g., PLGA); ligand-targeted liposomal formulations (e.g., folic-acid functionalization), and chemical conjugation to enhance solubility and receptor-mediated transcytosis. Mushroom compounds function by scavenging reactive oxygen species and modulating endoplasmic reticulum stress pathways to exert antioxidative effects; regulating lipid metabolism to maintain membrane integrity and mitochondrial function; and reducing neuroinflammation through the inhibition of NF-κB/MAPK signaling and the activation of Nrf2. Neurotrophic and neurogenic effects are mediated by NGF-stimulating erinacines/hericenones as well as TrkA receptors and Erk1/2 signaling, while the senolytic activity of triterpenoids

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demonstrates enhanced cell longevity. Mushroom extracts have shown some involvement in modulating GLP-1 pathways and serotonergic receptors which could suggest a use in metabolic and psychiatric disorders. These findings emphasize the potential of edible and medicinal mushrooms in dietary interventions and novel therapeutics for the purposes of targeting neurodegenerative disease and cognitive decline.

Keywords

Edible mushrooms · Neuroprotective · Neurogenesis · Neuroinflammation · Antioxidant · *Agaricus bisporus* · *Lentinula edodes* · *Pleurotus Ostreatus* · *Hericium erinaceus* · Vitamins · Micronutrients · Polysaccharides · Psilocybin · β-glucans · Triterpenoids · Erinacine A · Ergothioneine · Ergosterol

2.1 Introduction

Edible mushroom compounds have become a spark point of neuroscientific research due to their vast array of bioactive compounds and their potential to influence brain health through a variety of intersecting mechanisms. Neuroinflammation, characterized by the activation of microglia and the release of pro-inflammatory cytokines, is a critical factor in the progression of neurodegenerative diseases like Alzheimer's disease (AD). Understanding how mushroom-derived compounds influence these pathways offers valuable insights into potential therapeutic strategies.

The most widely consumed species globally, *Agaricus bisporus*, which includes white button, cremini, and portobello mushrooms, has been studied for its neuroprotective properties (García-Sanmartín et al. 2022). These mushrooms are notable for their content of compounds such as phenols, sterols, indoles, tyrosinase, and lectins, which together contribute to their antioxidant and anti-inflammatory effects (Ismaya et al. 2020; Gariboldi et al. 2023). These biochemical effects are also paralleled by positive modulation of the gut microbiome, supporting the increasingly recognized role of the gut–brain axis in neuroprotection (García-Sanmartín et al. 2022).

Lentinula edodes (shiitake), the second most popular edible mushroom mostly eaten in Asia, is also packed with phenolic compounds, ergothioneine, ergosterol, β-glucans, eritadenine, and lenthionine (Gariboldi et al. 2023). β-glucans in particular show the ability to preserve synaptic structure, reverse neuroinflammation, and improve memory and spatial learning in high-fat diet mouse models (Pan et al. 2021; Roszczyk et al. 2022). Anti-tumorigenic and anti-inflammatory modulation further highlight shiitake's therapeutic versatility (Dhasmana et al., 2025). *Pleurotus ostreatus* (oyster mushroom), a commonly eaten and nutritional species, have been shown to improve glucose metabolism, a mechanism mediated by β-glucans, and even counteract lead-induced neurotoxicity in rodents (Dicks and Ellinger 2020; Zhang et al. 2023). Polysaccharides from this mushroom species have demonstrated antiaging effects in the brain (Li et al. 2019).

Hericium erinaceus (lion's mane) is especially notable for its neurotrophic and neurogenic properties. Its polysaccharides protect against amyloid-β-induced neurotoxicity, a hallmark of Alzheimer's disease (Cheng et al. 2016), and its hericenones are thought to enhance cognition (Saitsu et al. 2019). Clinical data supports lion's mane's safety and its potential neurodegenerative therapeutics (Spelman et al. 2017; Docherty et al. 2023).

Other edible mushrooms, such as *Flammulina velutipes* (enoki), *Cantharellus cibarius* (chanterelle), and *Boletus edulis* (porcini) also show clinical potential. Enoki polysaccharides, especially when paired with ginsenosides, enhance cognition and reduce oxidative stress in Alzheimer's models (Zhang et al. 2018). Chanterelle is rich in β-glucans, lectins, selenoproteins, essential fatty acids, and minerals, with extracts showing promise in glioblastoma models (Kumar et al. 2024; Nowakowski et al. 2020). Porcini mushrooms, high in protein and minerals but low in fat, contain polysaccharides, phenolic antioxidants, and phytosterols, and have demonstrated the ability to restore gut microbiome balance, reduce inflammation, and increase short-chain fatty acid synthesis (Tan et al. 2022; Avram et al. 2023).

The neuroactive potential of less commonly consumed but therapeutically valued mushrooms is increasingly recognized. *Ganoderma lucidum* (reishi) polysaccharides and triterpenoids modulate neuroinflammation, enhance amyloid-β clearance, and support cognitive function by influencing cytokine profiles, microglial activity, and cellular pathways such as sphingolipid metabolism and autophagy (Cai et al. 2017; Hüseyin et al. 2017; Zeng et al. 2021). *C. militaris* supplies cordycepin, which reduces brain inflammation and white matter injury, and improves memory in Alzheimer's disease (AD) models (Wei et al. 2021; He et al. 2018). *Inonotus obliquus* polysaccharides promote amyloid-β degradation via the ubiquitin-proteasome system (Wang et al. 2023a). *Ophiocordyceps sinensis* delivers ergosterol, GABA, flavonoids, and phenolics with anti-inflammatory effects (Huang et al. 2024). *Grifola frondosa* (maitake) contains O-orsellinaldehyde, which reduces nitric oxide and pro-inflammatory signaling, shifting microglia toward neuroprotection and improving cognition in AD models (Tomas-Hernandez et al. 2021; Bai et al. 2019).

B vitamins are essential for brain health and are found in many mushroom species (Mikkelsen et al. 2024; Śliwiński and Gawlik-Kotelnicka 2024). Deficiencies in these vitamins are linked to cognitive impairment, AD, Parkinson's disease (PD), and psychiatric disorders (Liu et al. 2024; Zhang et al. 2024a; Marwaha et al. 2025). Mushrooms are also a rare non-animal source of vitamin D, specifically ergocalciferol, especially when exposed to ultraviolet (UV) light (Koyyalamudi et al. 2009; Mehrotra et al. 2014). Though the neurological impact of mushroom-derived vitamin D requires further study, its dietary presence is significant for populations at risk of deficiency.

Finally, mushroom metabolites such as β-glucans, ergothioneine, triterpenoids, and even ergot-derivatives (the basis for some migraine medications) represent a frontier for clinical neuroscience. β-glucans, for example, are major polysaccharides found in the cell walls of many mushrooms and are known for their antioxidant and anti-inflammatory actions, supporting neuronal survival and potentially

promoting neurite outgrowth and brain repair (Phan et al. 2015; Tong et al. 2023; Corso et al. 2021). The convergence of these findings highlights the remarkable potential of edible and medicinal mushrooms as sources of neuroactive compounds that could shape the future of brain health and disease intervention.

While many of the discussed compounds in this chapter are of importance medically, some challenges do exist in implementation. First of all, an effective method of extraction is key to ensure high yield, purity, and bioactivity of molecules of interest. Optimizing extraction determines whether key compounds like β-glucans, triterpenoids, and neuroactive terpenes retain their structure and function, which is critical for their efficacy in neurodegenerative disease models. Recent years have seen a shift from traditional hot water extraction to more sophisticated techniques such as response surface methodology (RSM), acid-base protocols, ultrasound- and microwave-assisted extraction, and enzyme-assisted extraction. In the case of RSM, it uses statistical modeling to map how variables like temperature, pH, and time interact, enabling researchers to maximize both yield and purity with fewer experimental runs (Szwengiel and Stachowiak 2016). Acid-base methods can enhance triterpenoid extraction but must be well-managed to avoid unwanted side reactions (Ruan et al. 2014). Cold aqueous extraction preserves heat-sensitive compounds, while ultrasound and microwave techniques accelerate extraction and minimize thermal degradation (Chemat et al. 2017; Mandal et al. 2007). Each method has unique advantages and limitations, making method selection crucial for targeting specific mushroom metabolites.

The second issue that must be faced is that of delivering these compounds to the brain, traversing the blood–brain barrier (BBB), and ensuring maximal bioavailability. This task has prompted the development of advanced bioavailability strategies. Current methods being explored include nanoparticle encapsulation, chemical conjugation, and ligand-targeted liposomal formulations (Kreuter 2014; Watanabe et al. 2012). These innovations are essential for translating the promise of mushroom-derived neuroactives into actual real-world therapies. Discussing extraction and bioavailability methods is key for maximizing compound recovery and for ensuring that these bioactives are able to meet their neural targets at effective dosages.

This chapter acts as an introduction into the clinical significance of edible mushrooms, their compounds of special interest, and their proposed mechanisms of actions. We also highlight the next step in the development process, looking into the extraction and bioavailability methods necessary for application, underpinning the future of mushroom-based interventions in brain health.

2.2 Edible Mushrooms of Interest

2.2.1 Commonly Consumed Edible Mushrooms

A. bisporus, the most common mushroom worldwide, is also a basidiomycete of the family Agaricaceae family. Because of its popularity, particularly in cuisine, it has been the focus for great attention from the academic point of view. The mushroom

possesses a few names, for example, portobello, chestnut, or button and is available in two immature forms: white (common, button) as well as the brown (cremini, chestnut) and a brown mature (portobello) type with an open cap (Gariboldi et al. 2023). It is rich in bioactive metabolites and proteins such as phenols, sterols, indoles, tyrosinase, and lectins (Ismaya et al. 2020). In mice studies, *A. bisporus* (white button) and *A. bisporus* brunnescens (portobello) represent potential sources of neuroprotective effect for the reduction of oxidative stress markers (IL-6, Nox-2, Hmox-1), improvement in the antioxidant capacity of these enzymes (catalase, superoxide dismutase), and a reduction in lipoperoxidation (García-Sanmartín et al. 2022). They were also described to exert beneficial effects on gut microbiota, which in turn would indirectly participate in neuroprotection through the gut–brain axis (García-Sanmartín et al. 2022). Another mouse experiment demonstrated that polysaccharides from *A. bisporus* mitigated the age-related decline in memory. Immunized mice presented an improvement in learning and memory, a decrease in the level of markers of oxidative stress, and improved gut microbiota and short-chain fatty acids composition (Duan et al. 2023). Studies conducted in porcine models also reported increased level of neurotransmitter precursors, threonine, glutamine, and methionine, alongside possibly enhancement of the brain function after consumption of *A. bisporus* (Solano-Aguilar et al. 2021).

L. edodes is the second most eaten mushroom in the world after *A. bisporus*. The original name of it was *A. edodes*, described by Berkeley in 1877, and there were many different names before its final name was designated (Song et al. 2025). It is now commonly known as Shiitake, and it is a mushroom native to East Asia. The mushroom contains several bioactive compounds, such as phenolic compounds, ergothioneine, ergosterol, eritadenine, β-glucans, and lenthionine, that have various health benefits (Gariboldi et al. 2023). The main bioactive compounds in *L. edodes* are β-glucans, which are believed to be responsible for their health-promoting effects (Roszczyk et al. 2022). β-glucans from *L. edodes* have been found to reverse the neuroinflammation effect caused by high-fat diet in mice, and ameliorate their memory recognition and spatial learning. Additional support for these β-glucans is their protection against synaptic architecture concomitant with dietary-induced neuroinflammation (Pan et al. 2021). The applications for which *L. edodes* is presumed to have potential are cancer therapy, infectious disease treatment, and treatment for autoimmune diseases (Roszczyk et al. 2022).

Another edible fungus in the Agaricaceae family is *P. Ostreatus*, commonly referred to as oyster mushroom (Gariboldi et al. 2023). *P. ostreatus* is associated with lower levels of triglycerides, low density lipoprotein, and total cholesterol. It has also demonstrated antihypertensive benefits and enhanced glucose metabolism (Dicks and Ellinger 2020). Both *Auricularia auricula* and *P. ostreatus* have been indicated to reduce lead-induced neurotoxicity in rodent models suggesting these as potential agents for reducing lead accumulation and elicited brain damage (Zhang et al. 2023). Acetylated polysaccharides from *P. djamor* were reported to ameliorate tissue damage in the aged mouse brain, decrease lipid peroxidation, and increase antioxidant ability, indicating potential antiaging effects (Li et al. 2019).

Hericium erinaceus has also gained a lot of interest for its neuroprotective properties. Studies have documented its positive impact on mood and cognitive function in healthy young adults (Docherty et al. 2023). Polysaccharides from *H. erinaceus* have been shown to protect against Aβ-induced neurotoxicity (Cheng et al. 2016). *H. erinaceus* has also gained a lot of interest for its neuroprotective properties. Studies have documented its positive impact on mood and cognitive function in healthy young adults (Docherty et al. 2023). Polysaccharides from *H. erinaceus* have been shown to protect against Aβ-induced neurotoxicity (Cheng et al. 2016). Hericenones are compounds that can be isolated from *H. erinaceus* and are believed to help with cognitive enhancement (Saitsu et al. 2019). The safety of *H. erinaceus* has been confirmed in clinical trials to support its potential application in neurological disorders such as PD, AD, and peripheral nerve injuries (Spelman et al. 2017).

Flammulina velutipes polysaccharides are capable of providing neuroprotective effects when combined with ginsenosides, which are a bioactive compound found in *Panax ginseng*. Together, they have demonstrated an ability to enhance cognitive function and reduce oxidative stress in mice displaying Alzheimer's disease deficits (Zhang et al. 2018). *F. velutipes* also safeguards against lead exposure by activating signaling pathways, which protect cells against oxidative stress and apoptosis, as well as influencing the gut microbiota (Liu et al. 2023).

Cantharellus cibarius, also known as golden chanterelle, is a commonly consumed edible mushroom native to Europe. *C. cibarius* has a high nutritional value, containing a good amount of carbohydrates and fiber, while having a low fat content. The mushroom also has potential medicinal properties as it contains β-glucans, lectins, selenoproteins, essential fatty acids, and a variety of minerals and vitamins (Kumar et al. 2024). Extracts from *C. cibarius* have shown potential in the treatment of glioblastoma (Nowakowski et al. 2020).

Boletus edulis (also known as Penny Bun mushroom) is another species of edible mushroom in the division basidiomycetes. It has a strong nutritional profile, full of proteins and minerals, while low in calories and fat. *B. edulis* contains numerous bioactive compounds with antioxidant, anti-inflammatory, and antineoplastic action. Some of the important bioactive compounds present in *B. edulis* include polysaccharides like β-glucans, phenolic compounds, and phytosterols (Tan et al. 2022). *B. edulis* has neuroprotective potential through alteration of the gut microbiota, as it was able to restore gut microbiome balance after antibiotic use. The mushroom also showed anti-inflammatory and antioxidant effects by reducing the levels of pro-inflammatory cytokines and increasing the production of short-chain fatty acids (Avram et al. 2023).

2.2.2 Uncommonly Consumed Mushrooms

Some mushrooms are not as commonly eaten in the human diet but are instead used primarily for their therapeutic benefits. *G. lucidum* polysaccharides (GLP) have shown reduced pro-inflammatory cytokines and increased anti-inflammatory cytokine levels in animal models. GLP also enhanced the phagocytic activity of

microglia, suggesting potential in the clearance of pathological proteins such as amyloid-β (Cai et al. 2017). Studies in Sprague-Dawley rats demonstrated that *G. lucidum* polysaccharides decreased malondialdehyde and myeloperoxidase levels, while increasing glutathione levels (Hüseyin et al. 2017). The antitumor potential of *G. lucidum* was explored in rats implanted with glioma cells, where polysaccharide treatment led to a reduction in tumor size and increased survival compared to untreated controls. The proposed mechanism involved increased CD8+ cytotoxic T cell activity, maturation of dendritic cells, and increased serum levels of interleukin-2, tumor necrosis factor-alpha, and interferon-gamma (Wang et al. 2018). Triterpenoids obtained from *G. lucidum* were linked with improved cognitive function and reduced neuronal apoptosis in mouse models. These effects were believed to be the result of regulation of sphingolipid metabolism and inhibition of telomere shortening, indicating potential for reducing age-related cognitive decline (Zeng et al. 2021).

The name *cordyceps* comes from the Greek word "kordyle" and the Latin suffix "stem," which translate to "club" and "head," respectively. For centuries, *Cordyceps* has been used as a tonic in traditional Chinese medicine. It was only in 1993 when it began to gain more attention globally after Chinese long-distance runners were able to set world records after consuming *Cordyceps sinensis* (Olatunji et al. 2018). *C. militaris* is the second most common *Cordyceps* mushroom after *C. sinensis* but is considered to be a cheaper alternative to its more popular counterpart. It is generally an uncommonly eaten mushroom that belongs to the phylum Ascomycetes and is mostly found in East Asia. It is used for both its medicinal and culinary properties (Zheng et al. 2024). The main bioactive compound found in *C. militaris* is cordycepin, and the mushroom has been used medicinally for its many studied properties including hypoglycemic, anti-inflammatory, hypolipidemic, and neuroprotective activity (Olatunji et al. 2018).

In a study utilizing mice with amyloid-β accumulation, polysaccharides from *I. obliquus* were found to enhance the activity of the ubiquitin-proteasome system. This resulted in a significant reduction in amyloid-β accumulation within the hippocampus (Wang et al. 2023a).

Active compounds isolated from *Ophiocordyceps sinensis* include ergosterol, gamma-aminobutyric acid (GABA), flavonoids, and phenolic compounds, all of which are believed to contribute to its anti-inflammatory properties (Huang et al. 2024).

Grifola frondosa (also known as Maitake or hen of the woods) is an edible and medicinal mushroom that is often found in Asia and North America. It contains the natural compound O-orsellinaldehyde, which has been shown to reduce lipopolysaccharide-induced nitric oxide production. It has also demonstrated an ability to suppress NF-kB and MAPK signaling pathways as well as promoting a shift in microglial polarization from a pro-inflammatory to an anti-inflammatory phenotype (Tomas-Hernandez et al. 2021). A protein-bound polysaccharide found in *G. frondosa* led to cognitive improvement and neuroprotection in mice models displaying Alzheimer's disease-like symptoms (Bai et al. 2019).

Antrodia cinnamomea is a rare edible mushroom that is also used for its medicinal properties. Studies using water extracts from these mushrooms on mice models have shown beneficial effects on obesity by modifying the gut microbiota, improving insulin sensitivity, and reducing inflammation (Chang et al. 2017). The antihepatoma effects of *A. cinnamomea* have been studied, with the mushroom targeting PI3/AKT-mediated cell cycle progression (Zhang et al. 2021).

2.2.3 Psychoactive Mushrooms

Psychoactive fungi have been used historically as traditional medicine in different cultures such as those of the Aztecs and Mayans. Psilocybin and psilocin, which are the main psychoactive alkaloids made by psychoactive mushrooms, have a similar structure to serotonin (Strauss et al. 2022). Historically, psilocybin-containing mushrooms were referred to by the Aztecs as *teonanacatl* ("god's flesh") and used in religious and healing ceremonies (Nichols 2020). Recently, research has been looking into the use of compounds found in psychoactive mushrooms as an alternative to conventional medication, to treat conditions such as anxiety, depression, and post-traumatic stress disorder (Plazas and Faraone 2023).

Psilocybe cubensis, commonly known as "magic mushroom," has recently emerged as a candidate for its potential neuropsychological benefits (Cavanna et al. 2022). Psilocybin, the main psychoactive compound in *P. cubensis*, is converted to its active form, psilocin, which then enters the systemic circulation and acts primarily through agonism at 5-HT2A receptors in the brain (Thaoboonruang et al. 2025).

Psychedelic use does not come without stigmatization especially seen during the 1900s in the United States. In 1970, psilocybin became a schedule I controlled substance in the USA, which can lead to issues regarding obtaining it for scientific research. Despite this, more recent studies showing the potential benefits especially in treating depression have made psilocybin the most studied classic hallucinogen (Lowe et al. 2021).

2.3 Compounds of Interest

2.3.1 Vitamins

B vitamins, B1 (thiamine), B2 (riboflavin), B5, B6, B9 (folate), and B12 are all essential nutrients for maintaining a healthy brain (Mikkelsen et al. 2024; Śliwiński and Gawlik-Kotelnicka 2024). Deficiencies in B vitamins have been associated with a wide range of neurological pathology, including cognitive impairment (Liu et al. 2024; Zhang et al. 2024a; Teixeira et al. 2025), Alzheimer's disease (Marwaha et al. 2025), PD-related seizures, Parkinson's plus syndrome (Poulidou et al. 2024), and mental health disorders (Śliwiński and Gawlik-Kotelnicka 2024) to name a few.

B1, and its more bioavailable derivative, benfotiamine, has been shown to improve learning and memory deficits via antioxidant and neuroprotective effects

(Mallika et al. 2025). Folic acid supplementation in cognitively impaired elders has also been shown to have a possible positive impact on cognition (Wang et al. 2024). B micronutrients seem to play an important role in healthy brain maintenance and mushrooms have been shown to be present in different mushroom species (Furlani and Godoy 2008). Folate has been found in the edible mushroom *F. velutipes* (Rezaeian et al. 2021). Riboflavin has been extracted out many species, such as in *Phellinus linteus*, *Lentinus edodes*, and *A. bisporus* (button mushrooms), *P. ostreatus* (Oyster Mushrooms), an *P. albidus* (Esteve et al. 2001; Cağlarirmak 2011; Contato et al. 2022). Limited research exists on the full presence of B vitamins and their extractability from mushrooms, which makes B vitamins an essential nutrient to assess in mushrooms.

Vitamin D deficiency is an issue prevalent in several chronic illnesses and among the general population (Mitchell et al. 2012; Amrein et al. 2020). A lipid soluble vitamin and steroid hormone, vitamin D plays an essential role in musculoskeletal health. However, research has also been shown to be an important player in neurological health and functioning, among other health benefits (Grant et al. 2025). Vitamin D levels and neurological impairment have consistently shown correlation in different disorders (Fu et al. 2024; Stavrogianni et al. 2025). In Alzheimer's disease, dementia, and cognitive impairment, vitamin D deficiency has been identified as a risk factor in all cases (Zhang et al. 2024b). Vitamin D supplementation, in some trials, has shown to improve cognitive impairment in the elderly (Zhou et al. 2023). These findings however are not fully conclusive (Montero-Odasso et al. 2023; Vyas et al. 2023).

Due to the vital role vitamin D plays, and the current increasing prevalence of deficiency in the global population, finding food sources of vitamin D, such as in mushrooms, is highly important. Ergocalciferol is a form of vitamin D found in food and has been an identified compound found in mushrooms treated with UV radiation (Koyyalamudi et al. 2009; Mehrotra et al. 2014; Leung and Cheung 2021). While the presence of ergocaliferol in edible mushroom species is confirmed, there is limited support for their ability to effect neurological health (Zajac et al. 2020).

While mushrooms contain many other micronutrients and vitamins, the vitamins discussed are the compounds of most interest found in mushrooms (Kozarski et al. 2015).

2.3.2 Edible Mushroom Metabolites

Metabolites, which are compounds produced within mushrooms due to different metabolic actions contain many compounds that are bioactive and of novel interest to neuroscientific research. Migraine medication such as ergot-derivatives are a perfect example of edible-mushroom metabolites applied in a modern clinical setting (Baron and Tepper 2010). Many other compounds are still in research to decipher their potential in clinical therapeutics. A potential compound to pay attention to is β-glucans, primarily β-(1,3)(1,6)-D-glucans, which are major polysaccharides found in the cell walls of mushrooms such as *P. ostreatus*, *G. lucidum*, and *H.*

erinaceus (Phan et al. 2015; Tong et al. 2023). The effect of interest in these species is as an antioxidant and anti-inflammatory, which protects neurons from oxidative stress and neuroinflammation (Corso et al. 2021; Wijesekara and Xu 2025). β-glucans may have the ability to reduce systemic and central nervous system inflammation via its immunomodulatory action, thereby having potential application to mediate disease progression in immune-mediated diseases such as Alzheimer's (Hu et al. 2022). Studies have also shown that β-glucans may be able to promote neurite outgrowth, preventing neuronal apoptosis, which would aid in brain repair mechanisms (Phan et al. 2015). For example, polysaccharides from *P. ostreatus* (POP) have demonstrated cognitive function improvements in Alzheimer's disease models, highlighting their therapeutic promise (Zhang et al. 2016).

Linoleic and linolenic acids are polyunsaturated fats found in mushrooms, which in animals play a role in maintaining neuronal membrane fluidity and function (McNamara et al. 2019). These fatty acids contribute to reducing neuroinflammation and oxidative stress, thereby supporting neuronal survival and cognitive function (Tan et al. 2024). Their role in brain health is significant, being involved in regulating cognition and neuropsychiatric presentation in the brain, complementing the effects of other mushroom bioactives (Kim and Song 2024).

Triterpenoids, a class of secondary metabolites found in mushrooms like *G. lucidum* and *Antrodia camphorata*, seem to exhibit strong neuroprotective effects (Zhao et al. 2023). An example compound is that of 2α-Hydroxyoleanolic acid (2α-HI), which reduces oxidative stress and neuronal apoptosis via activation of critical signaling pathway BDNF/TrkB/ERK/CREB and Nrf2 (Kou et al. 2022). These pathways promote neuronal survival and synaptic plasticity, which makes triterpenoids a noteworthy compound to consider in the development of dietary interventions for neurodegenerative disorders (Li et al. 2023). Lanostane-type triterpenoids from *I. obliquus* have also been shown to inhibit nitric oxide production in microglia, reducing neuroinflammation, an element in pathology (Jiang et al. 2024). This makes these triterpenoids highly interesting for its role in neurodegenerative disease management, as it may alleviate pathogenesis in diseases, such as Alzheimer's disease (Jiang et al. 2024).

Hericium erinaceus, Lion's mane, is a mushroom that has the neuroactive metabolites erinacines from its mycelium and hericenones from the fruiting bodies (Szućko-Kociuba et al. 2023). Studies show that erinacine A has the ability to promote neurite outgrowth and in turn, neurogenesis via the stimulation of nerve growth factor (NGF) synthesis (Hsu et al. 2023; Szućko-Kociuba et al. 2023). Erinacine A also acts as a neuroprotective agent in models of traumatic optic neuropathy, suppressing apoptosis and preserving vision (Hsu et al. 2023).

Erinacine S enhances neurosteroid accumulation, further supporting neurogenesis and preventing neuronal death (Lin et al. 2023). Hericenones similarly stimulate NGF synthesis and have been shown to be an effective agent in promoting brain health in neurological pathology models; clinical studies however have struggled in extrapolating these effects (Li et al. 2018).

C. militaris-derived cordycepin (3′-deoxyadenosine) is a multifunctional nucleoside that demonstrates an immunomodulatory effect, such as the reduction of neutrophil infiltration into the brain following traumatic brain injury, alongside decreased white matter injury (Wei et al. 2021). In models of amyloid-β-induced Alzheimer's disease, *C. militaris* administration led to a reduction in lipid peroxidation and nitric oxide levels, coupled with improvements in spatial memory in mice (He et al. 2018). Cordycepin seems to mediate these effects via the enhancement of cytokines and increasing CD4 and CD8 cell proliferation (Kang et al. 2015). This anti-inflammatory effect of cordycepin has been shown to reduce pain as well in joint-related pathology models (Ashraf et al. 2019). The multifaceted nature of cordycepin makes it a compound of interest in neurological disorders. Cordycepin significantly inhibits vascular cell adhesion molecule-1 and intracellular adhesion molecule-1 (VCAM-1 and ICAM-1, respectively), significantly reducing advancement of atherosclerotic lesions (Yan et al. 2017). Neuroprotection against ERK/CREB-mediated apoptosis has also been seen in cordycepin exposure in Aβ-hippocampal cell cultures (Zhou et al. 2025), suggesting promise as an AD therapeutic agent.

Ergothioneine and ergosterol, two bioactive molecules abundant in edible mushrooms, are of special interest due to their neuroprotective and anti-inflammatory properties. Ergothioneine is a potent antioxidant amino acid, particularly concentrated in mushrooms like *L. edodes* (Apparoo et al. 2025). Ergothioneine is involved in ROS scavenging, aiding in maintaining cellular redox balances that are essential for neuronal survival, especially in the context of neurodegenerative diseases (Ishimoto and Kato 2022).

Ergosterol, the principal sterol in fungi, also contributes to neuroprotection, though its mechanisms are still being elucidated. Present in mushrooms such as *L. edodes*, ergosterol is thought to stabilize neuronal membranes and reduce neuroinflammatory signaling. Some evidence suggests that ergosterol may modulate immune responses and support membrane integrity, thereby attenuating inflammation-induced neuronal injury (Gariboldi et al. 2023; Huang et al. 2024). Ergosterol in vivo has also been shown to promote neurite outgrowth and inhibit amyloid plaque formation (Sillapachaiyaporn et al. 2024). Many other beneficial effects have been attributed to Ergosterol (Rangsinth et al. 2023); however, for conclusive findings, more trials outside of animal studies and in-vitro models need to be performed to see their effects in patients and to better understand the complex mechanisms of action for each compound.

2.3.3 Psychoactive Compounds

The principal psychoactive in edible mushrooms is the alkaloids psilocybin and psilocin, which structurally share a similarity to endogenous serotonin (Plazas and Faraone 2023). Other tryptamines, such as baeocystin, norbaeocystin, and aeruginascin also show hallucinogenic effects, being potent metabolites (Sherwood et al.

2020). Psilocybe metabolites work their effect both via direct serotonergic action and allosteric interactions with dopamine and glutamate receptors (Waldbiling et al. 2023). This action on neurotransmitter balances has profound effects on the patient's mood (Romeo et al. 2025). The chemical composition of the fruiting bodies and micelia in psychoactive edible mushrooms differs, with psilocybin, baeocystin, norbaeocystin levels being significantly higher in fruiting bodies than mycelium (Waldbiling et al. 2023). The role for mushroom-derived psychotropics in medicine has been a growing field, especially in the treatment of psychiatric conditions (Strauss et al. 2022). In animal models, acute psilocybin administration enhanced cognitive flexibility (Torrado Pacheco et al. 2023), acted as an anxiolytic (Braun et al. 2024), and improved baseline functional network connectivity in models of alcohol use disorder (Reinwald et al. 2023).

In trials on humans, psilocybin was well-tolerated and did not show any short- or long-term detrimental effects to cognition or emotion processing (Rucker et al. 2022). These findings have been repeated in patient populations for major depressive disorder (Raison et al. 2023), alcohol-use disorder (Pagni et al. 2025), and bipolar disorder (McAllister-Williams et al. 2025).

Psilocybinis being theorized as a potential agent in AD treatment, as it counters the impairment in neuroplasticity seen in AD, this occurs by enhancing the natural neuroplasticity of the brain via the BDNF/TrkB and mTOR pathways, as well as having anti-inflammatory potential (Zheng et al. 2024).

Overall, alkaloid psychoactives from edible mushrooms are compounds of high potential with many different applications in neurotherapeutics. However, more trials and consistent findings need to be performed to determine their precise uses and to expose any adverse effects.

2.4 Extraction and Bioavailability Techniques

The successful delivery of the derived bioactivities of edible mushrooms into the central nervous system depends on two key cornerstones: (1) the optimized extraction method that preserves structural integrity and bioactivity, and (2) advanced techniques to traverse the blood-brain barrier (BBB).

2.4.1 Response Surface Methodology

Response surface methodology (RSM) combines regression modeling and factorial design to map the response surface of the yield from the extraction versus its key variables (Myers et al. 2016). The most common are the Box-Behnken and Central composite designs.

This can be applied to mushrooms, particularly in optimizing the β-glucan extraction from *P. ostreatus*. Based on preliminary trials, Szwengiel and Stachowiak (2016) had chosen four independent variables that are vital to yield and purity:
Temperature (X_1): 20–40 °C

HCl concentration (X_2): 1–6% (v/v)
Extraction time (X_3): 120–420 min
Agitation (X_4)**:** constant stirring (rate fixed)

They were able to estimate all quadratic and interaction terms while requiring fewer runs as they used a four-factor, three-level Box-Behnken design. By conducting 29 cycles, in all these cycles the design matrix itself was randomized to minimize any systematic bias.

$$Y = \beta 0 + i = 1 \sum 4 \beta iXi + i = 1 \sum 4 \beta iiXi2 + i < j \sum \beta ijXiXj$$

The model's accuracy and usability were confirmed by: ANOVA**:** $p < 0.0001$, and there was no significance in the lack of fit test ($R^2 \approx 0.97$) (Szwengiel and Stachowiak 2016).

3-D response surfaces and 2-D contour plots were generated to see how different pairings of the variables would affect the yield and deproteinization, helping to guide the study to the optimum conditions. Furthermore, a composite desirability function was implemented to allow them to both simultaneously maximize β-glucan yield and purity, allowing a "best compromise" to be achieved with the following conditions: 30 degrees Celsius, 3.8% HCI for 300 min, and have the solution stirred.

By using RSM to help determine conditions, a β-glucan yields seven times higher than hot water extraction alone (Szwengiel and Stachowiak 2016).

This methodology of extraction is optimum as it helps to minimize experiments and has a high predictive power as it helps to reveal variable interactions. However, the disadvantage is that it assumes a smooth response surface. As a result, the validity of the model is limited to the tested ranges only; as stated by Myers et al. (2016), it becomes complex when there are four or more variables.

2.4.2 Acid-Base Extraction

The mechanism is as follows: the acidic (pH 1–2) conditions cause the hydrolyzation of the ester and glycosidic bonds in the cell-wall polysaccharides, also dissolving pectins and proteoglycans. However during this process, consequent basification (pH 9–11) causes the target polysaccharides or protein complex to precipitate due to deprotonation of the target molecules (Ruan et al. 2014).

The case study titled "Extraction optimisation and isolation of triterpenoids from *G. lucidum*' by Ruan et al. (2014) explored three conditions in the extraction. First, hot water extraction (90 °C, 2 h), second, 0.1 M HCl pretreatment + hot water, and third, Acid–base protocol: 0.1 M HCl (60 min)→neutralization → 0.1 M NaOH (60 min).

Condition 3 had 1.8 times higher ganoderic acid content (quantified by HPLC at 254 nm) and a 20% increase in cytotoxicity (IC_{50} = 25μg/mL against HeLa cells) compared to hot water alone. However, there was increased risk of glycosidic bond cleavage and Maillard reaction (reaction between free amino groups and the reactive carbonyl groups of the reducing sugars), a risk which comes from prolonged

extremes of pH, leading to the generation of unwanted chromophores (Ruan et al. 2014).

One thing that can aid in the reduction of pH shocks would be to use buffering salts (citrate buffer), which can help in the mitigation of polysaccharide depolymerization via dialysis and rapid neutralization.

2.4.3 Hot Water Extraction

It would be a simple mechanism where it needs to be heated to 80–100 °C, allowing the solubility of the polysaccharide by disrupting the hydrogen bonds of the chitin–β–glucan matrices. The parameters to consider are the extraction time (1–4 h) and also the liquid-to-solid ratio (10:1 to 20:1), both of which will greatly influence the distribution of molecules and yield.

An example of this produced is in "*Lentinula edodes* Lentinan" where Chen et al. (2020) procured lentinan at 90 °C for 2 h at a 1:15 ratio, followed up by an overnight ethanol precipitation at 4 °C. Their results were 1.2% yield with demonstrated murine splenocyte proliferation (SI = 1.6 at 50μg/mL).

This methodology is great as it is simple, low cost, and needs minimal equipment; however, when applying this to mushroom extraction, the exposure to high temperatures for a prolonged time can result in the thermal degradation of small molecules (e.g., erinacines).

2.4.4 Successive Cold Aqueous Extraction

Preservation of Labile Compounds: This process occurs at 4–10 °C, thus the enzymatic and spontaneous oxidative degradation is decreased, helping to preserve low-molecular-weight neuroactive terpenoids, plus having 24-h macerations (3–5 cycles) leading to the accumulation of extract concentration.

Zhao et al. (2019) conducted five successive cold extractions with a 1:20 ratio, leading to a yield of crude erinacine fraction that caused 2.3 times upregulated mRNA in PC12 cells in comparison to the hot water extraction, which only had a 1.4X increase.

However, it does come with disadvantages: (1) extended timeline in comparison to the other methods, as five 24-h cycles have to occur, co-extraction of undesired proteins, necessity of large solvent volumes, and the need for chromatography for fractionation.

2.4.5 Ultrasound-Assisted Extraction

This is done using a technique called Acoustic Cavitation, where ultrasonic waves are used (20–40 kHz) to generate microbubbles that collapse, causing localized

shear forces and microjets. These forces disrupt the fungal cell walls and help to enhance solvent penetration (Chemat et al. 2017).

Chemat et al. was able to achieve 25% higher polysaccharide yield from the *C. militaris* at 200 W for 30 min at a 1:15 ratio, in comparison to when it was treated for a 2-h hot water extraction.

One consideration to have when scaling this up to an industrial level is that the high power densities risk partial depolymerization. To avoid this, however, you can do increments (e.g., 5 s on and 5 s off).

2.4.6 Microwave-Assisted Extraction

This uses dielectric heating, heating using a material that is a poor electrical conductor, at 2450 MHz coupled with polar solvent and sample matrices, which leads to rapid volumetric heating. As a result, you have a disruption in the hydrogen bonding, which leads to the acceleration of mass transfer (Mandal et al. 2007). Mandal et al. (2007) recorded that they achieved a 92% *A. blazei* β-glucan yield in 10 min at 500 W in comparison to the hot water extraction (3 h). Another benefit that was highlighted was that the shorter exposure minimizes thermal degradation, but the material of the heating apparatus needs to be chosen with caution in order to prevent hot spots. As a result, an adaptation such as rotation turntables will help to avoid nonuniform heating, helping to prevent an uneven extraction.

2.4.7 Subcritical Water Extraction

This methodology utilizes water at 100–374 °C, with the water pressure between 5 and 60 bar, as the water has a reduced dielectric constant, leading to the solubilization of moderately nonpolar compounds (Ibañez et al. 2003).

Ibañez et al. applied Subcritical Water Extraction to *Ganoderma applanatum* at 160 °C, 30 bar for 15 min, resulting in a 3× increase in the total triterpenoid concentration (HPLC-MS quantification) in comparison to a hot water extraction.

The clear benefits are a short extraction time and solvent-free operation, but it is very expensive to purchase those that can withstand the high pressure, as well as maintaining the safety protocols.

2.4.8 Enzyme-Assisted Extraction

The core of this methodology is to cause selective cell wall degradation by using enzymes to break down the polysaccharides in the cell-wall. Cellulases, hemicellulases, and pectinases are used to hydrolyze the β-1,4 and β-1,6 linkages, releasing all the entrapped bioactives. The conditions used for the reaction were the following: pH 4.5–6.5, 40–55 °C, enzyme load 1–3% w/w for 1–3 h.

Puri et al. (2012) used a pectinase and cellulase mix to extract *P. tuber-regium* polysaccharides, increasing the yield by 30% over a normal hot water extraction. A

note that was mentioned about this process is to make sure the enzymes deactivate post-reaction, by keeping them at 80 °C for 10 min.

2.4.9 Bioavailability Enhancement

Half the battle is efficient extraction, but a systemic delivery across the BBB needs the compounds to enhance solubility, protective labile structures, and exploit the receptor pathways to ensure efficient deliveries of the compounds. Nanoparticles such as the Poly(lactic-co-glycolic acid) (PLGA) are used to encapsulate β-glucans, which allows a sustained release and passive crossing via adsorption-mediated transcytosis into the BBB (Kreuter 2014). Another methodology is chemical conjugation, which helps to enable diffusion through tight junctions by increasing lipophilicity.

Surface modification of the molecules helps to reduce opsonization, allowing them to stay in blood circulation longer. Attaching ligands such as transferrin and lactoferrin allows it to attach to the BBB receptors, allowing the endothelial cells to engulf the particle and allowing it to reach the brain directly (Kreuter 2014).

2.4.10 Folic Acid-Targeting Ligand Liposomal Formulation

The BBB endothelial cells overexpress folate receptors α (FRα) and FRβ under inflammatory and neoplastic conditions (Lu and Low 2002). Thus, if you attach folic acid to the liposome surface, those cells that express folate on their membrane will bind the folic acid, causing receptor-mediated endocytosis, which allows the endosome to traffic the liposome containing the drug to the neuron (Watanabe et al. 2012).

Parameter	Optimal range	Impact on delivery
FA density (mol% of lipid)	0.3–0.7 (Lu and Low 2002)	Balances receptor binding vs. stealth
Liposome size	80–150 nm (Smith et al. 2018)	<150 nm favors paracellular and transcytosis
Surface charge (ζ-potential)	–5 to +5 mV (Kreuter 2014)	Near neutral avoids rapid clearance
Encapsulation efficiency (EE%)	≥70%	Ensures therapeutic payload
Lipid composition	DSPC:Cholesterol:DSPE-PEG 80:15:5 molar ratio (Watanabe et al. 2012)	Stability and fluidity control

Mechanism Pathway Summary:

1. Folic acid moiety engages FRα on luminal BBB surface.
2. Endocytosis of the liposome containing the biological compound results in the liposome being packaged into an endosome.

3. Transcytosis is the vesicular transport of the endosome across the endothelial cell.
4. Liposomal destabilization in acidic endosomes leads to the biological compound payload being released into the brain interstitium.

Watanabe et al. (2012) prepared FA-DSPE-PEG2000 conjugates, integrating 0.5 mol% FA into DSPC/cholesterol bilayers. These erinacine-rich extracts were then encapsulated, and after IV dosing (5 mg/kg erinacine equivalent) in mice, the brain concentration measured by LC-MS peaked at t 2.4μg/g tissue, 3.2× that of non-targeted liposomes ($p < 0.01$). In terms of behavior, the folic acid liposomes caused an improvement in a transgenic mouse model with Alzheimer's, shown by a 25% decrease in the escape latency when it completed the Morris Water Maze, indicating that there was a functional BBB crossing (Watanabe et al. 2012).

2.5 Proposed Biomechanisms of Edible Mushroom Compounds

2.5.1 Antioxidative Mechanisms

Oxidative stress is a central biochemical phenomenon in neuronal damage and eventual cell death, making antioxidative mechanisms a crucial element for brain health. 6-hydroxydopamine (6-OHDA) is a neurotoxin used in research to create PD models (Simola et al. 2007). This is done via the creation of ROS by disruption of mitochondrial functioning, generating reactive oxygen species (Glinka et al. 1997). Research into ergothioneine shows it has the ability to prevent overproduction of ROS in hypothalamic neurons treated with 6-OHDA, preventing cell death (Yuzawa et al. 2024). Neuronal death by 6-OHDA has been shown to be mediated by the endoplasmic reticulum (ER) response to stress, mimicking the pathological process found in PD (Ning et al. 2019). CAAT-enhancer-binding protein homologous protein (*Chop*) and growth-arrest and DNA-damage-inducible gene 34 (*Gadd34*), area is indicative of this response and upregulated in 6-OHDA-dependent neuronal death (Ning et al. 2019; Yuzawa et al. 2024). Both of these genetic markers of cell death are underexpressed when the neuron is pretreated with ergothioneine (Yuzawa et al. 2024). This neuroprotective nature, via antioxidative and antiapoptotic effects in 6-OHDA models proposes that it may serve as a method of therapeutics to aid in management of PD progression in patients. Furthermore, β-glucans and other mushroom polysaccharide extracts work as antioxidants by scavenging free radicals (Giese et al. 2015; Mirończuk-Chodakowska et al. 2021; Pérez-Bassart et al. 2023). *L. edodes* (shiitake) β-glucan showed an exceptionally high scavenging radical ability of 75.3% at a dose of 3.5 mg ml^{-1} and inhibition of α-amylase at 73.4%, suggesting antioxidant and antidiabetic properties (Yehia 2022). Shiitake β-glucans at higher concentrations also seem to negatively affect tumor cell viability and proliferation, inducing a potent immune response to cancer cells (Yehia 2022). Proteo-βglucan, derived from *G. frondosa* (Hen-of-the-wood) on transgenic mouse

models, have shown to effect multiple mechanisms underlying AD, increasing microglial recruitment to amyloid-β (Aβ) plaques, in turn increasing Aβ phagocytosis (Bai et al. 2019). We can also see positive antioxidant effects when coming to the neurotropic vitamins B1, B6, and B12 (Cuyubamba et al. 2025). Elevated ROS leading to activation of apoptotic pathways and finally neuronal death is mediated and protected when given this vitamin B combination in vitro, promoting neurite outgrowth mainly by promoting energy metabolism and cellular rebuilding, with B1 aiding in antioxidation (Cuyubamba et al. 2025). Proteomic studies into mushroom species *L. officinalis* and *G. frondosa* show proteins linked to ER-dependent unfolded protein response (UPR), a mechanism that aids in protecting the cell against oxidative stress (Abdelmoaty et al. 2024b).

2.5.2 Lipid Metabolism Effects

The brain's high energy demands and lipid-rich composition make lipid metabolism essential for neuronal survival, a role supported by mushroom-derived fatty acids (McNamara et al. 2019).

Polyunsaturated fatty acids (PUFAs), including linoleic and linolenic acids derived from edible mushroom species consist of properties that aid in neuronal membrane integrity and modulating neuroinflammatory processes (Günç Ergönül et al. 2013; McNamara et al. 2019; Bell et al. 2025). Fatty acids, such as linoleic and linolenic acids derived from mushrooms aid in energy production by supporting mitochondrial functioning and reducing oxidative damage, promoting the resilience and longevity of neurons (Sande et al. 2019; Liuzzi et al. 2023). Novel research, such as that done by Ali et al., found that mushroom-derived fatty acids may also play a role in modulating neuroinflammation in AD animal models (Ali et al. 2020). Infusion of linoleic acid showed a marked decrease in Aβ in Aβ-treated mice models, enhancing memory and synaptic function (Ali et al. 2020).

2.5.3 Anti-Inflammatory Mechanisms

Mushroom-derived compounds have garnered significant attention for their potent anti-inflammatory properties, which play a crucial role in protecting the brain from chronic neuroinflammation—a hallmark of many neurodegenerative diseases. Among these compounds, β-glucans found in species such as *P. ostreatus* and *G. lucidum* interact with immune cell receptors like dectin-1 to downregulate pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), while simultaneously promoting the release of anti-inflammatory cytokines such as interleukin-10 (IL-10) (Vetvicka and Vetvickova 2020). Cordycepin, a compound from *C. militaris*, has been shown to inhibit microglial overactivation, which is a key part of the inflammatory mechanism (Wei et al. 2021). This is done by inhibition of signaling pathways including nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK), thereby reducing

neuroinflammation in experimental models of Alzheimer's disease (Jakopovic et al. 2021; Wang et al. 2023b). Triterpenoids, particularly ganoderic acids isolated from *G. lucidum*, further contribute to anti-inflammatory effects by blocking NF-κB translocation to the nucleus, which curtails the expression of inflammatory mediators. At the same time, these triterpenoids activate the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway, enhancing the cell's antioxidant defenses and mitigating oxidative stress (Wang et al. 2023b). Collectively, these findings highlight a multi-targeted approach by which mushroom-derived bioactives modulate neuroinflammation and, in turn, support brain health.

2.5.4 Neurotrophic and Neurogenic Effects

As discussed earlier in this chapter, *H. erinaceus* compounds, notably erinacines and hericenones, demonstrate a significant neurotrophic ability through the stimulation of nerve growth factor synthesis (Martínez-Mármol et al. 2023). These metabolites promote neurite outgrowth primarily through activation of the TrkA receptor and downstream Erk1/2 signaling pathways, which are essential for neuronal survival and differentiation (Martínez-Mármol et al. 2023; Wong et al. 2012). Animal studies have provided findings suggesting neurogenesis and synaptic plasticity when treated with *H. erinaceus*, leading to improvements in learning and memory performance (Wong et al. 2012). For example, erinacine A administration in rodent models of neurodegeneration improved cognitive function and reduced neuronal loss (Li et al. 2018). These findings suggest that *H. erinaceus* secondary metabolites hold promise as therapeutic agents for neurodegenerative diseases by supporting neuronal growth and functional recovery.

2.5.5 Longevity Promotion

Mushroom-derived compounds have shown potential in modulating key biological pathways associated with aging and cellular senescence. Oxidative damage is also an important element contributing to neuronal aging and neurodegenerative pathology. Antioxidants such as mushroom-derivative ergothioneine play a critical role in protecting mitochondrial integrity, increasing cellular longevity (Cheah and Halliwell 2012). Senolytic agents have been an area of interest recently and are gaining more recognition as a possible therapeutic pathway for age-related health problems. Senescent cells have been associated with increased inflammation, mitochondrial dysfunction, DNA damage, and ROS production (Donovan et al. 2024). Triterpenoids have been shown to work as senolytic agents, reducing senescent cell levels, reducing inflammation (Abdelmoaty et al. 2024a) Triterpenoids have also been found to reduce apoptosis and enhance mitochondrial function, thereby promoting neuronal longevity (Wang et al. 2023a).

Mushroom proteins also upregulate glycolysis and energy metabolism, supporting sustained neuronal function and resilience under stress (Vetvicka and Vetvickova

2020), a crucial metabolic process for maintaining synaptic activity and plasticity during aging (Zhao et al. 2024). Moreover, some mushroom metabolites may induce hormetic effects, mild stress responses to ROS species that actually work to activate adaptive cellular defense mechanisms, thereby enhancing longevity and delaying neurodegeneration (Ristow and Schmeisser 2014).

Collectively, these mechanisms show promising candidates in edible mushroom-derivatives for therapeutic interventions aimed at promoting healthy brain aging and mitigating age-related cognitive degeneration.

2.5.6 Neurotransmitter and Synaptic Mechanisms

Emerging research indicates that some mushroom metabolites modulate key neuroreceptor systems such as glucagon-like peptide-1 secretion (GLP-1) and serotonin receptor signaling (5HTR), integral components of neuroprotection (Mehdi et al. 2023), mood regulation (Gong et al. 2025), and cognitive function (Pierret et al. 2025; Yamada et al. 2025). GLP-1 receptor agonists have been shown to exert neuroprotective effects by enhancing insulin signaling, which in turn mediates the activation of microglia, reducing neuroinflammation (Kopp et al. 2022). Oyster mushroom fortification in meals has been shown to beneficially influence GLP-1 pathways, potentially contributing to improved metabolic outcomes in patients with impaired glucose functioning (Dicks et al. 2022), evidently improving cognitive outcomes (Zeng et al. 2025).

5HTRs regulate mood, anxiety, and cognition (Yamada et al. 2025). Psychoactive edible mushroom species, containing psilocybin, appear to act as serotonergic modulators (Madsen et al. 2019), which could explain the traditional use of psychedelic mushrooms in mood enhancement and anxiety reduction (Griffiths et al. 2016). By influencing these receptor systems, psychoactive metabolites may offer novel therapeutic avenues for neuropsychiatric disorders and neurodegenerative diseases characterized by disrupted neurotransmission (Griffiths et al. 2016; Haniff et al. 2024; Wiens et al. 2024). One interesting mechanism of mushroom metabolite protective effects seen is in 5HTR-dependent modulation of microglia by psilocin (Wiens et al. 2024). This novel finding proposes psilocin, and its phosphorylated mushroom-derivative form psilocybin should be considered as a drug candidate for treatments of neurodegenerative disease, where microglia reactivity contributes to inflammation and neuronal fibrosis and death (Wiens et al. 2024).

Further studies are needed to elucidate the molecular interactions and clinical relevance of the discussed effects, but the modulation of GLP-1 and serotonergic signaling represents two promising frontiers in mushroom-based neurotherapeutics.

2.6 Conclusion

To summarize, medicinal and edible mushrooms are multifaceted and copious resources for both neurorestorative and neuroprotective management. Throughout this chapter, we progressed from an acknowledgment of the huge taxonomic diversity, varying from the globally ubiquitous *A. bisporus* and *P. ostreatus* to the more niche *H. erinaceus*, *G. lucidum*, *C. militaris*, and other specialized species, to a detailed examination of the key bioactive compounds they contain. Molecules, including β-glucans, erinacines/hericenones, cordycepin, triterpenoids, essential vitamins (D & B complex), ergosterol, and ergothioneine, collectively form a combined attack against inflammation, age-related neuronal decline, and oxidative stress. This is achieved by their functional complementarity and structural variety, which support a span of biochemical action—from boosting endogenous antioxidant enzymes and preserving mitochondrial function to scavenging free radicals and the modulation of endoplasmic reticulum stress pathways.

Delivery and extraction methodology aid in the maximization of both the bioactivity and yield while aiming to overcome any biological barriers. Traditional hot water and acid-base protocols are still vital for polysaccharide extraction till this day, but with the technological age comes the rise of new advanced methods, such as response surface methodology, ultrasound- and microwave-assisted extraction, subcritical water processing, enzyme-assisted protocols, and successive cold macerations. All of these methods have illustrated significant improvements in both purity and potency. From a pharmacological point of view, the ligand-targeted liposomal formulations (such as folic acid-functionalized vesicles) and nanoparticle encapsulation (e.g., PLGA) have shown great advancement in passing the blood–brain barrier. These delivery methods can ensure receptor-mediated uptake, enhanced CNS bioavailability, and sustained release. This can be achieved by adjusting parameters like surface charge, particle size, and encapsulation efficiency.

Mechanistically, mushroom-derived compounds enact a multi-targeted approach to neuroprotection. The B-vitamins neutralize reactive oxygen species and assist in downregulating pro-apoptotic genetic programs and the mediation of the antioxidant actions by β-glucans and ergothioneine. Consequently, it allows safeguarding neurons against toxins such as 6-hydroxydopamine. Lipid-modulating fatty acids support the membrane integrity and aid in mitochondrial respiration, while the anti-inflammatory agents readjust the microglial activity through inhibition of F-κB/MAPK signaling and activation of Nrf2 pathways. The erinacines and hericenones stimulate TrkA/Erk1/2 pathways and nerve growth factor synthesis, helping to foster neurite outgrowth, cognitive resilience, and synaptic plasticity. Additionally, there has been increasing evidence for hormetic and senolytic properties (the majority due to triterpenoids), which gives clear evidence of their ability to promote cell longevity, attenuate chronic inflammation, and clear senescent cells.

Beyond the traditional neuroprotective mechanisms, particular mushroom metabolites interact with metabolic and neurotransmitter systems. The *Pleurotus* species modulates the secretion of glucagon-like peptide-1, indicating a link between glycemic control and neuronal health, while the engagement of the

serotonergic receptor by psychoactive alkaloids paves a pathway into mood regulation, microglial modulation, and anxiety reduction. These findings underline the potential of mushroom-derived compounds in battling cognitive declines in neurodegenerative disorders such as AD and PD, psychiatric conditions, and metabolic syndromes, which co-occur with the decline in the individual's cognition.

To apply all of these findings to a clinical environment, it will require strict, extensive human trials where there is a manageable delivery system and standardized extraction protocols. Key tasks of these proposed trials include ensuring compound stability, minimizing side effects, establishing clear long-term safety profiles, and determining optimal dosing regimens. Furthermore, the intricate interplay among varied mushroom metabolites suggests that instead of having isolated compounds, a whole extract formula may have advantages; it could have harmonious interactions that we are yet to observe. Furthermore, advances in the world of computational modeling, receptor-targeted engineering, and omic technology will assist in the refinement of multi-agent interventions and result in patient-tailored management.

In conclusion, the alliance of mycology, pharmaceutical technology, and neurobiology has portrayed edible mushrooms as a viable frontier in brain health research. Mushrooms' abundance of bioactive compounds, partnered with newfound delivery and extraction methods, sets the foundation for innovative therapeutics aimed at enhancing neuroregeneration and preventing cognitive decline. With the implementation of laboratory discoveries into clinical applications, both medicinal and edible mushrooms stand to make a significant impact on the field of integrative neurotherapeutics.

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Introducing the Best Medicinal Mushrooms for Brain Health

3

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Abstract

There is massive interest in the use of natural and functional foods as medicinal products. This growing interest has spotlighted medicinal mushrooms as potent allies for enhancing brain health. These medicinal mushrooms have attracted massive attention in recent years for their remarkable potential to support brain health and cognitive function. This presents a comprehensive overview of select mushroom species that demonstrates significant neuroprotective, cognitive-enhancing, and adaptogenic properties in the emerging category of brain-boosting superfoods. This chapter explores the cognitive and neuroprotective benefits of key species, including Lion's Mane (*Hericium erinaceus*), Reishi (*Ganoderma lucidum*), Cordyceps (*Cordyceps militaris*), Chaga (*Inonotus obliquus*), Maitake (*Grifola frondosa*), and Turkey Tail (*Trametes versicolor*). They contain bioactive compounds such as beta-glucans, triterpenes, hericenones, and cordycepin, which support brain health through multiple mechanisms. Lion's Mane stimulates nerve growth factor (NGF) production, enhancing neurogenesis and memory. Reishi modulates stress responses and improves sleep via its adaptogenic and anti-inflammatory effects. Cordyceps boosts mitochondrial function and mental endurance by increasing ATP synthesis. Chaga's high antioxidant capacity mitigates oxidative stress, while Maitake regulates glucose metabolism and neuroinflammation. Turkey Tail supports the gut–brain axis, promoting cognitive stability through prebiotic effects. Preclinical and clinical

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studies highlight their potential in addressing neurodegenerative conditions, such as Alzheimer's and Parkinson's diseases, though further standardized human trials are needed. As global interest in integrative approaches to brain health continues to gain awareness, this chapter underscores the importance of medicinal mushrooms as accessible, sustainable, and scientifically validated nutraceuticals based on continued research, hence it serves as a comprehensive introduction for researchers, clinicians, and health-conscious individuals seeking natural interventions to support mental clarity, cognitive function, and overall brain vitality as emerging superfoods in modern neuroscience and nutritional therapy.

Keywords

Medicinal mushroom · Neuroprotection · Brain health · Traditional medicine · Superfood · Nutritional therapy

3.1 Introduction

Mushrooms are a good source of dietary fiber, which is made up of both soluble and insoluble fiber. Chitin (about 5 g/100 gDM) and oligosaccharides β-glucans are the most common parts of the insoluble fraction; however, heteropolysaccharides such as pectineus substances, hemicellulose, and polyuronides make up 10–50% of DM (Zhao et al. 2022). The role of mushrooms has been richly documented throughout human history, from the early Greek, Egyptian, Roman, Chinese, African, and Mexican cultures as both food and medicine (Torres-Gómez 2023; Zázik and Daňová 2022; Brothwell and Brothwell 1998; Khanna and Sharma 2013). They have been used since the Paleolithic period (about 2.5 million years ago to 10,000 B.C.) (Samorini 2012; Hardy et al. 2018), and their use has historically been linked to spiritualism. There are about 3–6 million species of fungi around the world, but only about 3–8% of them have been accurately and precisely identified (Wasser 2010; Hawksworth and Lücking 2017). In addition to selenium (Spaulding and Beelman 2003), fiber, and a number of other vitamins and minerals, mushrooms are an uncommon source of ergothioneine (Haytowitz et al. 2008). Preclinical and clinical research indicates that mushrooms may have effects on cancer risk, weight control, oral health, and cognitive function (Smith et al. 2002; Lam-Sidun et al. 2021; Narayanan et al. 2023). According to preliminary data, mushrooms may interact with the gut microbiota to promote the development of adaptive immunity and better immune cell function, thereby supporting healthy immune and inflammatory responses. Apart from their direct nutritional and health benefits, mushrooms are linked to higher dietary quality, according to an analysis of data from the US food intake survey (Feeney et al. 2014). By stimulating the brain and preventing the shrinkage of neurons in the cortex, prophylactic substances such as lentinan from lentinula, cordycepin from cordyceps, and hericenones from mushrooms and erinacines from lion's mane mycelium help reduce stress, promote sound sleep, and improve memory (Arya 2022). Additionally, preliminary sensory research indicates

that lower-sodium dishes and mushrooms mixed with meats are popular and may help cut back on red meat consumption. This chapter discusses medicinal mushroom, its properties, and significance in brain health. It further outlines the role of the bioactive constituents in memory and cognitive function. Furthermore, this study is vital as a non-pharmacological intervention in the treatment response of neurodegenerative diseases and neurological illnesses.

3.2 Understanding Medicinal Mushroom and Their Boasting Properties

Mushrooms have been an important ingredient in traditional medicine for the past century, and as a healing tool for a variety of diseases including cognitive deficits (Chang and Buswell 2022). Its importance has become a special area for scientists, in examining its mechanisms, properties, components, and functions in influencing neurogenesis, synaptic plasticity, and mitochondria function (Arya 2022; Chong et al. 2021). Unlike conventional edible mushrooms, medicinal species such as *Hericium erinaceus* (Lion's Mane), *Ganoderma lucidum* (Reishi), *Cordyceps militaris*, and *Inonotus obliquus* (Chaga) contain unique metabolites that exert neuroprotective and nootropic effects. Bioactive compounds found in medicinal mushrooms include triterpernes, phenolic compounds, herinones, cordycepin, adenosine, erinacines, beta-glucans, and antioxidants. Beta-glucans in Reishi and Shiitake mushrooms enhance immunomodulatory function, reduce chronic inflammation, conserve the gut barrier, and limit pro-inflammatory lipopolysaccharides (Fijałkowska et al. 2022; Young et al. 2024). Triterpenes, lipid-soluble compounds with anti-inflammatory and antioxidant properties, are found in chaga and Reishi plants. They inhibit microglia cells and limit pro-inflammatory cytokines, making them potential therapeutic agents for neuroprotection. Triterpenes also protect the blood–brain barrier from harmful substances. Lion's Mane contains hericenones and erinacines, responsible for producing brain-derived neurotrophic factor and nerve growth factor, crucial for memory and learning. Conversely, synaptic plasticity is supported by BDNF. Lion's Mane stimulates neurogenesis, in the hippocampus, vital for memory consolidation, by upregulating these neurotrophic factors. By modifying adenosine receptors (A1, A2A, and A3), cordycepin (3′-deoxyadenosine), a bioactive nucleoside present in *C. militaris*, demonstrates neuroprotective effects (Yin et al. 2022; Tung et al. 2025). Adenosine receptors are crucial in regulating cerebral blood flow, the release of neurotransmitters, and neuroinflammation. Studies have found that cordycepin improves mitochondrial function by increasing ATP production and lowering oxidative stress, thereby improving energy metabolism (Das et al. 2021; Sharma et al. 2023). Additionally, it exhibits anti-ischemic properties, protecting neurons from hypoxia-induced damage. Mushrooms such as Chaga and Reishi are rich in phenolic acids (e.g., protocatechuic acid, gallic acid) and melanin, which possess strong free radical-scavenging capabilities (Peng and Shahidi 2022; Fan 2024; Łysakowska et al. 2023). Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) and endogenous antioxidants,

is a major contributor to neuronal degeneration. Phenolic compounds neutralize ROS and upregulate endogenous antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GPx), thereby preserving neuronal integrity (Iqbal et al. 2024; Ryang et al. 2021; Kou et al. 2022). Hericenones and erinacines from Lion's Mane stimulate neurogenesis in the hippocampus by activating the PI3K/Akt and MAPK/ERK signaling pathways, which are upstream regulators of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (Ratto 2022). Concurrently, BDNF facilitates long-term potentiation (LTP), a cellular mechanism underlying learning and memory, by increasing dendritic spine density and synaptic strength (Chong et al. 2021; Szućko-Kociuba et al. 2023; Kinderlehrer 2025). Chronic neuroinflammation is a hallmark of neurodegenerative disorders. Medicinal mushrooms mitigate this via multiple pathways, such as Beta-glucans, reducing systemic inflammation and indirectly lowering CNS inflammation (Tan et al. 2021a, b; Silva et al. 2023). Triterpenes inhibit NF-κB signaling, a master regulator of inflammatory responses (Han et al. 2021; Ruan et al. 2021; Wu et al. 2021). Cordycepin suppresses microglial activation, preventing excessive cytokine release (Liu et al. 2022; Govindula et al. 2021). Neurons are highly dependent on mitochondrial ATP production. Cordycepin and adenosine optimize mitochondrial efficiency by enhancing oxidative phosphorylation and reducing ROS generation (Tan et al. 2021a, b; Wang et al. 2024). Reishi's triterpenes further support mitochondrial biogenesis via activation of the PGC-1α pathway, which is critical for maintaining neuronal energy homeostasis. The gut microbiota influences brain function through the production of neurotransmitters (serotonin, GABA) and microbial metabolites (short-chain fatty acids). Mushroom polysaccharides act as prebiotics, fostering beneficial gut bacteria such as *Bifidobacterium* and *Lactobacillus* (Törős et al. 2023; Balakrishnan et al. 2021). A healthy gut microbiome reduces systemic inflammation and enhances the production of neuroprotective metabolites, thereby supporting cognitive function. Medicinal mushrooms represent a pharmacologically rich resource for enhancing brain health through multi-targeted mechanisms (Akinola et al. 2025; Bell et al. 2025). Their bioactive compounds ranging from beta-glucans and triterpenes to hericenones and cordycepin work synergistically to promote neurogenesis, synaptic plasticity, and mitochondrial function while suppressing neuroinflammation and oxidative stress.

3.3 The Best Medicinal Mushrooms for Brain Health

3.3.1 Lion's Mane (*Hericium erinaceus)*

H. erinaceus or Lion's Mane and Pompom mushroom are a source of nutritional constituent for brain health. They are white, filamentous mushrooms that grow almost exclusively on hardwood trees and are native to North America, Europe, and Asia (Spelman et al. 2017). They are commonly referred to as Yamabushitake in Japanese and Monkey Head mushroom in Chinese. The *H. erinaceus* fungus has been utilized as a memory booster by traditional practitioners for centuries,

particularly to boost memory (Thongbai et al. 2015). Lion's Mane is special among other medicinal mushrooms due to the capacity to defend and rebuild cells of neurons. Contemporary science has revealed its promise in reducing symptoms of Alzheimer's disease (Friedman 2015; Spelman et al. 2017). Scientists' research also validates the prospects of Lion's Mane's in the synthesis of NGF, a protein, which is accountable for neuronal repairs and regeneration (Kawagishi et al. 1991; Trovato et al. 2016).

Key Bioactive Compounds

Lion's Mane is a medicinal mushroom that has two significant bioactive compounds, i.e., hericenones and erinacines (Hao-Yu et al. 2015). Hericenones are present in the fruiting body of the mushroom and can be extracted from the basidiocarps, whereas erinacines are typically found in the mycelium, the root-like part of the mushroom (Chaiyasut and Sivamaruthi 2017). These compounds were proven to be potent NGF inducers in neurons (Lai et al. 2013; Kawagishi et al. 1991; Cheng et al. 2016). Nerve growth factor or NGF is important in the survival and development of neurons and participate in learning and memory. Especially, erinacines, and more specifically erinacine A, have been thoroughly investigated and have been known for their extraordinary ability to induce NGF and for their ability to penetrate the blood–brain barrier (Kawagishi et al. 1994; Lee et al. 2000). Also, these compounds are of absolute relevance to mitigate brain inflammation and reverse oxidative stress, processes that result in cognitive decline and brain aging (Kushairi et al. 2019).

Mechanism of Action

(i) *Stimulates Nerve Growth Factor (NGF) for Neurogenesis*

Lion's Mane supports brain health mainly by increasing the production of NGF. NGF helps neurons grow, survive, and repair themselves. Both hericenones and erinacines are relatively hydrophobic compounds with low-molecular weight, and have been proven to stimulate nerve growth factor (NGF) synthesis and promote NGF-induced neurite outgrowth in nerve cells in vitro (Lai et al. 2013). In laboratory studies, extracts from Lion's Mane promoted NGF gene expression in human astrocyte cells (Mori et al. 2008). In animal studies, it also increased NGF levels in the hippocampus; the part of the brain responsible for memory (Kuo et al. 2016).

(ii) *Enhances Synaptic Plasticity and Cognitive Function*

Synaptic plasticity, the ability of the brain to change and form new connections, is essential for learning and memory. Lion's Mane can enhance plasticity by supporting the development of new nerve connections and protecting neurons from damage (Zhang et al. 2016). These effects have been linked to improved memory, learning, and overall cognitive performance in animal models.

(iii) *Supports Memory Retention and Learning*

In Alzheimer's disease models, Lion's Mane is found to reduce the buildup of harmful amyloid-beta plaques, protect the neurons, and improve performance on memory tests (Mori et al. 2009). Its polysaccharides and diterpenoids also help reduce brain inflammation and slow down the loss of neurons (Cheng et al. 2016). These effects suggest that Lion's Mane may not only show cognitive decline but also improve brain function over time.

Scientific Studies and Clinical Trials of Lion's Mane
Research from animal models has shown the potential of Lion's Mane in preventing age-related decline. Alzheimer's symptoms in mice improved after daily intake of Lion's Mane, demonstrating NGF expression and improving spatial memory and visual recognition (Mori et al. 2009). Similarly, mice administered erinacine A from Lion's Mane had reduced inflammation, reduced brain lesions after a stroke (Zhang et al. 2016), and provided protection from neurodegeneration. Subjects of a clinical trial involving Japanese adults between the ages of 50 and 80 who were suffering from mild cognitive impairment and were administered 250 mg of Lion's Mane (with 96% dried fruiting body) thrice a day for 16 weeks had significant improvement in their Hasegawa Dementia Scale scores. However, this improvement was lost following withdrawal of supplements, suggesting that continuous supplementation may be necessary (Mori et al. 2009). In another vein, participants who were given cookies containing 0.8 g of Lion's Mane fruiting body per day for 12 weeks enhanced short-term memory (Saitsu et al. 2019). A 2020 study by Li et al., in which mycelium capsules rich in erinacine A were administered, patients with early Alzheimer's improved in cognitive decline after 49 weeks of treatment. Although further research is required, these studies indicate that Lion's Mane can be a beneficial herbal supplement for elderly individuals experiencing memory loss or cognitive decline.

Consumption Lion's Mane is available in several forms, each with its own benefits, including capsules, extracts, teas, and fresh mushrooms. Capsules are popular because of their convenience and consistent dosing, while dual extracts use both water and alcohol to pull out all the beneficial compounds, which may be more effective for therapeutic use. Dried mushroom slices are also boiled to make tea, and fresh mushrooms can also be cooked and eaten in meals. However, for the most reliable cognitive benefits, capsules and extracts are generally recommended, as they deliver higher and more consistent amounts of the mushroom's active compounds. Overall, the most effective form depends on personal preference, dosage needs, and intended brain health goals.

3.3.2 Reishi (*Ganoderma lucidum)*

Reishi mushroom is native to parts of Asia, North America, and Europe (Wasser 2004). It is scientifically known as *G. lucidum*, and traditionally called "Lingzhi" in China, and "Reishi" in Japan. In traditional Asian medicine, it has been used for centuries to promote vitality and improve longevity. Reishi grows on hardwood trees and is easily recognized by its reddish-brown, glossy cap and woody texture (Wachtel-Galor et al. 2011). *G. lucidum* is valued primarily for its medicinal benefits and is often referred to as the Mushroom of Immortality (El Sheikha 2022; Ekiz et al. 2023; Plosca et al. 2025). The mushroom is particularly known as one of the most powerful adaptogens, enhancing the body's response to stress (Khatian and Aslam 2018). Modern research continues to explore and support the therapeutic properties of *G. lucidum*, highlighting its potential to reduce symptoms of anxiety, improve mood, and promote better sleep (Venturella et al. 2021).

Bioactive Compounds

The therapeutic potential of *G. lucidum* or Reishi is attributed to three key bioactive compounds: triterpenes, polysaccharides, and beta-glucans, which are responsible for its anti-inflammatory, anticancer, hepatoprotective, antioxidant, and antidiabetic properties (Zhou et al. 2007; Wu et al. 2013; Wu et al. 2019; Wang et al. 2019; Kou et al. 2021; Swallah et al. 2023). The extraction of triterpenes is usually performed using methanol, ethanol, acetone, chloroform, ether, or a mixture of these solvents (Masyita et al. 2022). Triterpenes are known for their calming and anti-inflammatory effects, which contribute to mood stabilization and stress reduction (Choi et al. 2014). Polysaccharides, extracted from the body, spores, and mycelia of *G. lucidum*, and beta-glucans enhance immune function and offer neuroprotective benefits by fighting oxidative stress and inflammation in the brain (Boh et al. 2007; Dinesh Babu and Subhasree 2008).

Mechanism of Action

(i) *Adaptogenic properties*

Reishi is considered a powerful adaptogen because of its ability to help the body regulate stress responses. Its triterpenes, particularly ganoderic acids, modulate the hypothalamic-pituitary-adrenal (HPA) axis, reducing excess cortisol production. By regulating cortisol and supporting the adrenal glands, Reishi creates a state of physiological balance that enhances the body's resistance to physical and emotional stress (Wachtel-Galor et al. 2011). Additionally, studies suggest that Reishi may influence neurotransmitters such as serotonin and dopamine, which play a role in mood and anxiety regulation, possibly through its impact on monoamine oxidase activity and neuroinflammation reduction (Ahmad et al. 2021; Khatian and Aslam 2018).

(ii) *Anti-inflammatory effects*

The triterpene and polysaccharide compounds in Reishi reduce anti-inflammation by inhibiting pro-inflammatory cytokines like TNF-α and IL-6 and upregulating anti-inflammatory mediators. Triterpenoids such as ganoderic acid downregulate the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in microglial cells, which are central to the inflammatory response in the brain (Choi et al. 2014). This anti-inflammatory mechanism protects the neurons from oxidative stress and degeneration, creating a neuroprotective environment that supports cognitive function and emotional well-being.

(iii) *Enhances sleep quality and relaxation for cognitive health*

Experimental studies in animal models have shown that extracts from *G. lucidum* can increase non-rapid eye movement (REM) sleep duration by acting on GABAergic pathways and possibly through the modulation of serotonergic systems (Cui et al. 2012). Additionally, its adaptogenic role in lowering cortisol supports a natural circadian rhythm, which promotes deep, restful sleep. Improved sleep quality in turn contributes to better memory consolidation, mood regulation, and overall mental clarity (Ahmad 2018).

Scientific Studies and Clinical Trials of REISHI (Ganoderma lucidum)

Several studies support Reishi's role in stress reduction and mental clarity. In a randomized controlled trial involving sedentary college students, participants receiving 1000 mg of *G. lucidum* daily for 30 days exhibited significant improvements in anxiety, depression, vitality, and overall psychological well-being compared to the placebo group (Mitra et al. 2024). These findings suggest that *G. lucidum* supplementation can effectively reduce psychological stress and enhance mental clarity in humans. Moreover, animal studies show that Reishi extracts increase serotonin and norepinephrine levels and reduce corticosterone, indicating its ability to regulate mood and stress through HPA axis and monoamine pathways (Zhao et al. 2021). *Ganoderma lucidum*, or Reishi, exhibits significant neuroprotective properties through its anti-inflammatory and autophagy-enhancing effects. In a study focusing on neuroinflammation, *G. lucidum* polysaccharide (GLP) treatment reduced the expression of pro-inflammatory cytokines and chemokines in microglial cells (Cai et al. 2017). Additionally, in both *Caenorhabditis elegans* and human cells, Reishi extracts promoted longevity by enhancing autophagy and downregulating mTOR signaling, the key mechanisms involved in aging and cellular health (Peng et al. 2021).

Consumption

Reishi is commonly consumed in tinctures, capsules, and teas because they are effective methods for delivering concentrated levels of triterpenes and polysaccharides. Capsules offer convenience and consistent dosing, while teas provide a traditional, calming method for daily use. Because of its rough texture and bitter taste, Reishi is rarely eaten fresh but is widely available in supplement form (de Mattos-Shipley et al. 2016).

3.3.3 Cordyceps (*Cordyceps Sinensis and Cordyceps Militaris)*

Fungi and Insects have been pivotal in traditional Chinese medicine in the treatment of illnesses and poison. *Cordyceps* is a parasitic type of fungus, used as a natural and renewable source of energy; it is traditionally found on the larvae of insects and is mostly from the high-altitude regions of China, Tibet, and Nepal, where it is native (Joshi et al. 2017). While *C. Militaris* and *C. Sinensis* are the two primary species, *C. Militaris* is more commonly used due to the higher accessibility (Jędrejko et al. 2021; Kala et al. 2023; Ontawong et al. 2024). *Cordyceps* are waiting to be verified as a therapeutic agent for brain health since they have the potential to foster the cell's energy besides the fact that they can increase ATP within the nucleus (the body's energy). Similarly, it would appear that ATP enables energy transfer between cells and thus is vital for neuroprotective pathways (Joshi et al. 2017; Choi et al. 2020; Das et al. 2021; Rawat et al. 2024).

Bioactive Compounds

The most prominent bioactive compounds present in *Cordyceps* are cordycepin (3′-deoxyadenosine) and adenosine (Tuli et al. 2014). Cordycepin exhibits structural features similar to adenosine, a nucleoside involved in energy metabolism and neurotransmission. In addition, cordycepin also exhibits antioxidant, anti-inflammatory, and neuroprotective properties that support cognitive resilience (Zhou et al. 2025). Together, the cordycepin and adenosine compounds in *Cordyceps* interact with purinergic receptors in the brain to increase ATP synthesis, enhance mitochondrial function, and regulate inflammatory responses (Das et al. 2010; Tuli et al. 2014).

Mechanism of Action

(i) *Increases ATP production and brain energy metabolism*

Within the cell, cordycepin is phosphorylated to form cordycepin monophosphate (CoMP), which mimics AMP and activates AMP-activated protein kinase (AMPK). Activation of AMPK enhances mitochondrial biogenesis and increases ATP synthesis, thereby improving cellular energy metabolism, particularly in neurons and muscle cells (Hawley et al. 2020). This mechanism supports brain energy metabolism, especially in high demand states such as fatigue, cognitive strain, or aging.

(ii) *Enhances mental endurance and cognitive performance*

Cordyceps have also been found to improve endurance and mental focus by protecting the brain from oxidative stress and regulating neurotransmitters such as dopamine and acetylcholine. Acidic polysaccharides extracted from *C. militaris* have been shown to activate the PI3K/Akt and Nrf2 signaling pathway. Activation of Nrf2 leads to the upregulation of heme oxygenase-1 and other antioxidant enzymes, which protect the neurons from oxidative stress-induced damage (Bai et al. 2022). This mechanism contributes to improved endurance and cognitive performance.

(iii) *Supports blood circulation and oxygen delivery to the brain*

Extracts from *Cordyceps* promote nitric oxide production, improving vasodilation and blood flow, facilitating better oxygen and nutrient delivery to the brain (Ji et al. 2009). *Cordyceps* have also been shown to increase erythropoietin (EPO) levels, a hormone that stimulates red blood cell production. More red blood cells improve oxygen carrying capacity, leading to better oxygenation of brain tissue.

Scientific Studies on Cordyceps (Cordyceps Sinensis and Cordyceps Militaris)
Recent studies highlight Cordyceps' potential in mitigating fatigue and enhancing cognitive function (Choi et al. 2020). Research have demonstrated that acidic polysaccharides from *C. militaris* improved learning and memory in mice experiencing exercise-induced fatigue. This effect was mediated through the PI3K/NRF2/HO-1 pathway, which plays a crucial role in antioxidant defense mechanisms (Bai et al. 2022). Additionally, a 2018 study found that *Cordyceps* polypeptides enhanced cognitive performance in mice with induced memory impairments. The treatment improved oxidative stress markers and regulated neurotransmitter levels, suggesting a protective effect on the nervous system (Yuan et al. 2018). *Cordyceps* also shows promise in neuroprotection as revealed in a study by He et al. (2018), ethanol extract from *Cordyceps militaris* was administered in a mouse model of Alzheimer's disease induced by amyloid-beta peptides. The extract reduced oxidative stress and improved memory performance in behavioral tests. Furthermore, findings from a recent study show that cordycepin conferred neuroprotection to catecholaminergic PC12 neuronal cell cultures exposed to Aβ1–42-insult by reducing the production of reactive oxygen species, restoring the mitochondrial membrane potential, and inhibiting apoptosis (Zhou et al. 2025). In cases of cerebral ischemia, *C. sinensis* extract (CSE) was found to alleviate neuronal damage by regulating mitochondrial respiratory functions and inhibiting apoptotic pathways (Bai et al. 2020). Findings from the same study also reveal that CSE also reduced oxygen-free radical (OFR) and improved ATP levels.

Consumption of Cordyceps (Cordyceps Sinensis and Cordyceps Militaris)
Cordyceps is commonly available in powder, capsules, and tea forms. However, for therapeutic or cognitive benefits, extracts rich in cordycepin and adenosine are preferred for maximum efficiency (Elkhateeb and Daba 2022).

3.3.4 Chaga (*Inonotus obliquus)*

Chaga mushroom, scientifically known as *I. obliquus*, is a slow-growing parasitic fungus found primarily on birch trees in cold climates like Siberia, Northern Canada, and parts of Northern Europe. Often referred to as the "King of Medicinal Mushrooms," Chaga has a rich history in ancient medicine, especially in Russia and other parts of Eastern Europe, where it has been used as a remedy for inflammation, gastrointestinal disorders, and longevity. In recent years, Chaga has gained

recognition in research for its remarkable antioxidant and neuroprotective properties (Xin et al. 2021). It also has one of the highest known ORAC (Oxygen Radical Absorbance Capacity) scores among natural foods, supporting the body against oxidative stress (Gobert 2024).

Bioactive Compounds

The neuroprotective effects of Chaga can be attributed to three primary bioactive components; polyphenols, melanin, and betulinic acid (Camilleri et al. 2024a). Polyphenols are strong antioxidants that neutralize free radicals and support cellular integrity in brain tissues. It suppresses neuroinflammation and improves memory, learning, and cognitive function (Vauzour 2012). Chaga contains a unique form of melanin that enhances antioxidant enzyme activity and may shield brain tissue from UV and environmental stress (Debnath et al. 2013). Betulinic acid is a compound derived from the birch tree host. It possesses anti-inflammatory, antitumor, and anti-amyloid properties (Han et al. 2019).

Mechanism of Action

(i) *High antioxidant capacity reduces oxidative stress in the brain*

Chaga's remarkable antioxidant properties are primarily attributed to its rich content of polyphenols and melanin. The compounds activate the Nrf2 (nuclear factor erytgroid 2-related factor 2) signaling pathway, leading to the upregulation of antioxidant enzymes such as heme oxygenase-1 (HO-1), superoxide dismutase (SOD), and catalase (CAT). This, in turn improves antioxidant effects and prevents the generation of reactive oxygen species (ROS) (Lin et al. 2023).

(ii) *Anti-inflammatory effects for neuroprotection*

Many neurogenerative conditions are attributed to chronic neuroinflammation. Extracts from Chaga have been shown to suppress pro-inflammatory cytokines IL-β, IL-6, and TNF-α, which are often elevated in aging brains and neurodegenerative conditions. Additionally, in a study using murine BV2 microglial cells, an inotodiol-rich Chaga extracts significantly reduced the expression of IL-β, IL-6, and TNF-α highlighting its potent anti-inflammatory effects (Sajeev et al. 2024; Ban et al. 2025).

(iii) *Potential for reducing amyloid plaque formation*

Amyloid-beta (Aβ) plaques are protein aggregates commonly found in the brains of individuals with Alzheimer's disease. Chaga's bioactive compounds, particularly its polysaccharides, have shown potential in reducing Aβ accumulation through the activation of the Nrf2/HO-1 pathway, which regulates oxidative stress responses and protein-folding defenses (Han et al. 2019).

Scientific Studies on CHAGA (Inonotus obliquus)
A 2021 study found that Chaga extracts improved spatial memory and neuronal damage in aging rats. These changes were linked to decreased inflammatory markers and improved antioxidant defenses in hippocampal brain tissue (Xin et al. 2021). Another in vitro study found that Chaga protected PC12 neuronal cells against β-amyloid-induced toxicity by inhibiting reactive oxygen species and cell viability (Han et al. 2019). Although human trials are still limited, the mechanistic evidence from animal and cellular models suggests that regular Chaga supplementation could offer long-term neuroprotective benefits and delay cognitive decline associated with aging.

Consumption of CHAGA (Inonotus obliquus)
Chaga is most commonly consumed as a tea, made by simmering dried mushroom chunks in water to extract its antioxidants. Powdered extracts can be added to coffee or smoothies, while capsules are convenient for daily use. However, for maximum benefits, most people look for products labeled as dual extracts, which include both water-soluble and alcohol-soluble compounds.

3.3.5 Maitake (*Grifola frondosa)*

Grifola frondosa, or Maitake is a functional mushroom native to China and Japan. This edible wood-decay mushroom is found growing on oaks and chestnuts, and is widely recognized for its immune-stimulating, antitumoral, antidiabetic, anti-allergic, antioxidant, antiaging, and neuroprotective effects (Rossi et al. 2018; Wu et al. 2021; Tripodi et al. 2022). They are also known as "hui-shu-hua" or "grey tree flower," because of their distinctive appearance (Wu et al. 2021). Maitake has garnered scientific attention for its potential in regulating glucose metabolism, modulating immune responses, and enhancing neuroplasticity, which are all crucial factors in maintaining cognitive health (Yeh et al. 2011; Han and Cui 2012; Bai et al. 2019; Tripodi et al. 2022).

Bioactive Compounds
The therapeutic effects of Maitake are attributed to two bioactive compounds; β-glucans and polysaccharides. Polysaccharide compounds isolated from Maitake, exhibit multiple physiological and health promoting antitumor, anti-inflammation, and immunomodulation effects (He et al. 2017). Studies have found that the polysaccharides, which were extracted from Maitake, could improve cognitive function via inhibiting oxidative stress (Chen et al. 2017). The immune activity of polysaccharides regulates the body's immune functions, and proteo-β-glucan, a polysaccharide bioactive component of Maitake, possesses neuropharmacological activity as well (Bao et al. 2016; Meng et al. 2019; Bai et al. 2019).

Mechanism of Action

(i) *Supports glucose metabolism and brain energy balance*

Maitake polysaccharides have been shown to improve insulin sensitivity and regulate blood glucose levels (Preuss et al. 2012). In diabetic rat models, specific fractions like GF5000 enhanced insulin receptor sensitivity, leading to improved glucose uptake and utilization. This regulation of glucose metabolism ensures a steady energy supply to the brain, essential for optimal cognitive function (Xiao et al. 2015).

(ii) *Modulates immune responses affecting cognitive function*

The immunomodulatory effects of Maitake are evident in its ability to modulate cytokine production and enhance immune cell activity. Studies have shown that Maitake extracts can reduce neuroinflammation by suppressing pro-inflammatory cytokines like TNF-α and IL-6 in microglial cells (Tomas-Hernandez et al. 2021; Rowaiye et al. 2022; Yoon 2025). By mitigating neuroinflammation, Maitake contributes to the preservation of cognitive functions.

(iii) *Enhances brain plasticity through metabolic regulation*

In addition to its neuroinflammatory properties, Maitake influences brain plasticity by modulating metabolic pathways. Research indicates that Maitake extracts activate the DAF-16/FOXO and SKN-1/NRF2 signaling pathways, which are associated with increased expression of brain-derived neurotrophic factor (BDNF) and antioxidant enzymes (Aranaz et al. 2021). These changes promote neuronal growth, synaptic plasticity, and resilience against oxidative stress.

Scientific Studies on MAITAKE (Grifola frondosa)

Research by Manohar et al. (2002) revealed that a natural water-soluble extract obtained from maitake mushroom favorably impacts glucose/insulin metabolism in insulin-resistant KK mice. Additionally, a 2019 study investigating the effects of Maitake polysaccharides on Alzheimer's disease models found that PGM improved learning and memory impairments, reduced neuron loss, and alleviated amyloid-beta plaque accumulation in the hippocampus (Bai et al. 2019). These findings suggest that Maitake's regulation of insulin signaling pathways contributes to its neuroprotective properties. Emerging research indicates that Maitake polysaccharides not only improve insulin sensitivity, but also enhance cognitive performance in diabetic models. In a study by Xiao et al. (2021), diabetic mice administered with Maitake extract, known as GF5000, exhibited significant improvements in insulin resistance, which facilitated better glucose uptake in the brain, to ensure a stable energy supply for cognitive processes. Another factor that contributes to cognitive

decline in metabolic disorders is oxidative stress. Fan et al. (2019) found that a polysaccharide extract from Maitake ameliorated learning and memory function in mice with aluminum chloride-induced amnesia. The extract's antioxidant properties reduced oxidative damage in the brain, thereby enhancing cognitive performance.

Consumption
Maitake can be incorporated into diet through a variety of forms, including capsules, tinctures, and soups, which allow for gentle extraction of water-soluble compounds, especially beta-glucans.

3.3.6 Turkey Tail (*Trametes Versicolor)*

Trametes versicolor, also called Turkey Tail, is a multicolored striped medicinal mushroom that is valued for its robust health effects. It is called "kawaratake" in Japanese, and "Yunzhi" in traditional Chinese medicine (PDQ Cancer Information 2020). Turkey Tail is revered for its immune-boosting and adaptogenic properties and role on the gut–brain axis, a critical communication network connecting gastrointestinal health and brain function (Jayachandran et al. 2017; D'Amico et al. 2021). Neuroscientific research has further illustrated that Turkey Tail mushrooms possess antioxidant qualities, which can serve as neuroprotectants (Alzheimer's Drug Discovery Foundation 2021). The evidence indicates that Turkey Tail's therapeutic promise is in its ability to prebiotically restore microbial balance, decrease neuroinflammation, and modulate immune responses, all of which collectively promote enhanced cognitive function and neurological resilience, especially in instances of inflammatory or degenerative disease (Benson et al. 2019; Venturella et al. 2021; Darshan et al. 2024).

Bioactive Compounds
Two major constituents define Turkey Tail's powerful health benefits: Polysaccharopeptides (PSP) and beta-glucans. PSP is a unique protein-bound polysaccharide known for its immunoregulatory and antitumor effects (Saleh et al. 2017). Specifically, Polysaccharide K (PSK) is the active compound in Turkey Tail mushrooms (Ma et al. 2017). Beta-glucans, on the other hand, act as prebiotics, supporting the growth of beneficial gut bacteria such as *Lactobacillus* and *Bifidobacterium*, while suppressing harmful strains like *Clostridium* and *Staphylococcus* (Yu et al. 2013). Both compounds serve as key drivers of gut–brain communication and immune system regulation.

Mechanism of Action

(i) *Prebiotic effects for gut microbiome support*

The gut microbiome plays a crucial role in overall health, influencing digestion, immunity, and even brain function (Wu and Wu 2012; Goto and Ivanov 2013;

Galland 2014). Turkey Tail influences the composition of the gut microbiota by promoting beneficial bacteria. This activity enhances intestinal barrier function and supports the production of neurotransmitters such as GABA and serotonin, which are essential for mood regulation and cognitive stability (Jayachandran et al. 2017; Saleh et al. 2017).

(ii) *Modulates the gut–brain axis to influence cognitive function*

The effects of *Trametes versicolor*, or Turkey Tail mushroom extends to the central nervous system through regulation of the gut–brain axis. The gut–brain axis is a bidirectional communication system between the gastrointestinal tract and the central nervous system. When gut microbiota interacts with the host brain, its mechanism influences the pathology of neuropsychiatric disorders (Martin et al. 2018; Naveed et al. 2021). Turkey Tail improves brain function by altering bacterial profiles that influence the neural signaling pathways, including the vagus nerve and neuroinflammatory mediators (Sarkar et al. 2016).

(iii) *Strengthens immune function for overall brain health*

Research by Benson et al. (2019) reveals that Turkey Tail enhances innate and adaptive immunity through its polysaccharopeptide, which stimulates natural killer cells, macrophages, and T-lymphocytes. These immune effects are vital for clearing neurotoxins, suppressing inflammation, and preventing cognitive decline. Studies suggest that *Trametes versicolor* activates neuroprotective pathways involving nuclear factor erythroid 2-related factor 2 (Nrf2) and reduces oxidative stress and glial inflammation in models of traumatic brain injury and neurodegeneration (D'Amico et al. 2021, 2023).

Scientific Studies on Turkey Tail (Trametes Versicolor)

Turkey Tail has been reported to be beneficial to the gut microbiome (Lye et al. 2016; Saleh et al. 2017). D'Amico et al. (2021) demonstrated Turkey Tail extract reduced hippocampal neuroinflammation and oxidative stress in a model of traumatic brain injury and its function for post-trauma cognitive dysfunction (D'Amico et al. 2021). A study in 2013 of human fecal microbiota showed that *T. versicolor* extract modulated gut microbiota through increasing populations of *Bifidobacterium* and *Lactobacillus* while inhibiting pathogenic bacteria like *Clostridium* and *Staphylococcus*. These beneficial bacteria ameliorated gastrointestinal symptoms like diarrhea, improved digestion and gut-derived neurochemical signaling, lowered cholesterol, reduced the risk of certain cancers, improved immune system function, and improved digestion (Yu et al. 2013). Additionally, Camilleri et al. (2024b) identified that Turkey Tail mushrooms are antibacterial against various prevalent pathogens, including *Staphylococcus aureus*, *Escherichia coli*, and *Listeria*. Furthermore, chronic inflammation and immune dysfunction have commonly been linked to illnesses such as Parkinson's and Alzheimer's diseases. Research by Paola et al. (2023) demonstrated that Turkey Tail can suppress neuroinflammatory processes,

regulate α-synuclein levels, and maintain redox balance in models of Parkinson's disease (Paola et al. 2023). Moreover, its capacity to induce heat shock proteins and vitagenes that are components of cell defense is evidence of its potential as a nutritional neurotherapy for age-related cognitive decline (Scuto et al. 2024). Moreover, a study of patients with Meniere's disease—a condition that impacts the inner ear and is linked to cognitive symptoms—indicated that supplementation with Turkey Tail resulted in better cognitive function and less oxidative stress (Bell and Fernandes 2023).

Consumption of Turkey Tail (Trametes Versicolor)
Turkey tail mushrooms are primarily consumed in the form of tea or hot water extracts to deliver immune-modulating compounds. Turkey Tail is also prepared for consumption as a powder from the fungal mycelium and its fermented substrate. It may also be taken as capsules for convenient dosing of polysaccharopeptides (PSP) and beta-glucans. For brain and immune support, a combination of mycelium and fruiting body extracts is recommended, as both demonstrate synergistic effects (Benson et al. 2019) (Table 3.1).

Future Directions The current research on medicinal mushrooms highlights their immense potential in supporting brain health, and several areas require further exploration. Future studies should prioritize standardized clinical trials to establish optimal dosages, long-term safety, and efficacy in humans. Currently, much of the evidence emerge from preclinical or small-scale human trials, necessitating larger, placebo-controlled studies to validate cognitive benefits. Another critical direction is the development of enhanced extraction methods to maximize bioavailability. For instance, dual-extraction techniques (water and alcohol) for compounds like triterpenes in Reishi or hericenones in Lion's Mane could improve therapeutic outcomes. Research should explore synergistic combinations of mushrooms, such as Lion's Mane and Cordyceps, for cognitive enhancement. The gut–brain axis is underexplored, but Turkey Tail and Maitake show promise in modulating gut microbiota. Personalized mushroom supplements based on genetic predispositions could revolutionize preventive care. Sustainability and cultivation must be addressed, with advances in fermentation technology ensuring consistent potency while reducing environmental impact.

3.4 Conclusion

Medicinal mushrooms, rich in bioactive compounds like beta-glucans, triterpenes, and hericenones, have been found to improve cognitive health. These fungi work on various pathways, including reducing neuroinflammation, boosting neurogenesis, improving mitochondrial function, and supporting the gut–brain axis. Lion's Mane, Reishi, Cordyceps, Chaga, Maitake, and Turkey Tail are all beneficial for memory, nerve regeneration, stress management, mental energy, and immune system health. However, strict human trials are needed to ensure these benefits can be used in

Table 3.1 Comparison of the cognitive functions of medicinal mushrooms

Mushroom	Key bioactive compounds	Cognitive benefits	Mechanism of action
Lion's Mane (*Hericium erinaceus*)	Hericenones, Erinacines, Beta-glucans	Enhances memory and learning	Stimulates NGF production for neuron growth
		Stimulates neurogenesis	Upregulates BDNF for synaptic plasticity
		Reduces symptoms of Alzheimer's	Reduces amyloid-beta plaques
Reishi (*Ganoderma lucidum*)	Triterpenes, Polysaccharides, Beta-glucans	Reduces stress and anxiety	Modulates HPA axis to lower cortisol
		Improves sleep quality	Anti-inflammatory via NF-κB inhibition
		Neuroprotection	Enhances GABAergic pathways
Cordyceps (*Cordyceps militaris*)	Cordycepin, Adenosine, Polysaccharides	Boasts mental endurance	Activates AMPK for mitochondrial energy
		Enhances ATP production	Improves oxygen delivery via nitric oxide
		Protects against ischemia	Reduces oxidative stress
Chaga (*Inonotus obliquus*)	Polyphenols, Melanin, Betulinic acid	High antioxidant capacity	Activates Nrf2 pathway for antioxidant defense
		Reduces neuroinflammation	Suppresses pro-inflammatory cytokines
		Prevent amyloid plaques	Modulates amyloid-beta accumulation
Maitake (*Grifola frondosa*)	Beta-glucans, Polysaccharides	Supports glucose metabolism	Improves insulin sensitivity for brain energy
		Enhances neuroplasticity	Activates BDNF via DAF-16/FOXO pathways
		Reduces neuroinflammation	Suppresses TNF-α and IL-6
Turkey Tail (*Trametes versicolor*)	Polysaccharopeptides (PSP), Beta-glucans	Supports gut–brain axis	Acts as a prebiotic for beneficial gut bacteria

regular medicine. The future of mushroom-based neurotherapeutics depends on standardizing extracts, finding sustainable sources, and creating personalized formulations.

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Medicinal Mushrooms and Their Effects on Memory and Cognitive Function

4

Kevin Thomas Mathew

Abstract

Medicinal mushrooms have long been utilized in traditional medicine and are currently gaining scientific interest for their potential role in supporting cognitive health. This chapter explores the neuroprotective effects of key mushroom species like *Ganoderma lucidum* (Reishi), *Hericium erinaceus* (Lion's Mane), and *Cordyceps* species, thus focusing on their impact on memory, neuroplasticity, and cognitive function. These mushrooms are rich in bioactive compounds that could contribute to neuroprotective effects. Mechanisms discussed include Brain-Derived Neurotrophic Factor (BDNF) and nerve growth factor (NGF), enhancement of cerebral energy metabolism and regulation of gut–brain axis, which are crucial for neuronal growth, survival, and synaptic plasticity. Additionally, these compounds exhibit strong antioxidant and anti-inflammatory properties like targeting signaling pathways of NF-κB and Toll-like receptors to reduce oxidative stress and neuroinflammation, two major contributors to age-related cognitive decline.

Current findings from preclinical and emerging clinical studies are reviewed to provide an insight into their cognitive potential, especially in the aging populations. This chapter aims to provide a foundational understanding of how medicinal mushrooms may contribute to cognitive health by highlighting both their traditional roots and evolving modern scientific relevance.

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Keywords

Cognitive function · Medicinal mushrooms · Neuroprotection

4.1 Introduction

Mushrooms are a group of large, filamentous fungi that have been incorporated into the human environment for hundreds of years (Jo Feeney et al. 2014). Their nutritional value has always been well regarded, and its role in human health has expanded. Today, mushrooms are valued not only as functional foods but also for reflecting their medicinal properties through nutritional supplements, nutraceuticals, and fungal therapy products, thus playing an important role in the healthcare system (Venturella et al. 2021).

Cognitive function includes learning, attention, and the ability to solve problems. These are essential for day-to-day life and the overall well-being of a human being. Cognitive function is not completely unavoidable, and there are signs of decline by the age of 60 in overall cognitive abilities (Glisky 2007). Various factors may contribute to cumulative brain damage, with an increase in age leading to multiple cognitive impairments. These factors may include cerebral ischemia, head trauma, or the onset of degenerative diseases such as Alzheimer's disease (AD) (Murman 2015). Recent studies suggest that the regular consumption of medicinal mushrooms may benefit cognitive health, particularly in aging populations. Bioactive compounds found in mushrooms such as various polysaccharides, ergothioneine and polyphenols have been associated with various neuroprotective effects, which include antioxidant and anti-inflammatory properties thus maintaining a helpful cognitive function. This chapter explores the role of medicinal mushrooms in cognitive and memory function by highlighting their history, key bioactive constituents, the various properties of medicinal mushrooms, and current evidence from preclinical or clinical studies.

4.2 Medicinal Mushrooms: An Overview

Medicinal mushrooms have always held an important role in human civilization and culture for thousands of years. They are recognized not only for their nutritional value but also for their therapeutic properties they exhibit. Their collective history, general properties, and classification all reflect a field that is both deeply rooted in tradition and rapidly evolving with progress in scientific advancements. The medicinal use of mushrooms dates back to antiquity, evidenced across numerous continents and civilizations.

Archaeological findings such as "Mushroom Stones" from Guatemala, dated about 3000 years old, suggest that mushrooms were featured in the early medicinal or mystical rituals, and classical texts from Greek and Roman writers like Hippocrates and Pliny refer to various species and their applications. Psychoactive

mushrooms were used as edibles during the ancient Chinese, Japanese, and Eastern European medicines seen in *Ganoderma Lucidum* (Reishi or Ling Zhi) and *Lentinula edodes* (Shiitake) appear in texts, which show traditional therapies that combine the use of dietary and curative practices. Mushroom species like *Inonotus obliquus* (Chaga), *Fomitopsis officinalis* (Agaricon), and *Piptoporus betulinus* (Birch Polypore) were used to treat diverse medical conditions that ranged from gastrointestinal disorders to various cancers and infectious diseases, which were seen in Eastern Europe (Molitoris 1994).

Despite their long history, only a fraction of the world's mushrooms has been studied. Out of 150,000 species in the world, only about 15,000 have been described scientifically. While early knowledge was focused on empirically observed effects, modern research increasingly validates ancient claims and uncovers newer medicinal properties through scientific investigation and clinical trials (Wasser 2011).

4.3 Medicinal Mushrooms and Cognitive Functions

Cognitive function represents the tangled output of the brain's complex machinery. Maintaining optimal cognitive performance throughout the lifespan is a significant aspect of human health. Medicinal mushrooms owe their value to specialized chemicals called bioactive compounds, which handle all the health effects observed in people.

They range from polysaccharides, terpenoids, phenols, heterocyclic amines, and fungal immunomodulatory proteins (FIPs). Polysaccharides (especially beta-glucan) are complex carbs that are made of long chains of sugar molecules. They are studied immensely because of their ability to boost the immune system, help fight tumors, and reduce inflammation in the body. Terpenoids are natural chemicals found both in plants and mushrooms that have very strong biological effects, such as killing bacteria, fighting viruses, and reducing the risk of cancer. Phenols are antioxidant compounds that help protect cells from damage caused by free radicals and reduce inflammation (Németh et al. 2025).

- Neurotropic Factor Modulation:

These are proteins that support the survival, growth, and differentiation of various neurons. They are critical for brain development, synaptic plasticity, and total cognitive function. Among the well-studied research is the brain-derived neurotrophic factor (BDNF). BDNF supports neuronal health and is heavily involved in learning and memory processes. Certain species of medicinal mushrooms are hypothesized to promote the synthesis and secretion of neurotrophic factors, such as BDNF and nerve growth factor (NGF). Elevated or increased levels of these factors can contribute to enhanced synaptic function, neurogenesis, and overall neuronal resilience. This modulation represents a direct biomechanical pathway through which mushrooms might help support the functional and structural integrity required for optimal cognition (Li et al. 2018a, b; Jahshan et al. 2017; Kim et al. 2020).

- Antioxidant and Anti-inflammatory Pathways:

Oxidative stress and neuroinflammation are two significant contributors to age-related cognitive decline and neurodegenerative diseases (Musella et al. 2018; Vaidya and Mandalika 2015). Chronic inflammation in the brain is often mediated by the activation of glial cells as microglia and astrocytes, which release pro-inflammatory cytokines and reactive oxygen species (ROS) that might damage neurons and disrupt any form of synaptic communication (Vaidya and Mandalika 2015; Pan et al. 2018). As mentioned earlier, phenols and polysaccharides are medicinal compounds that are rich in antioxidants, which can help neutralize free radicals and reduce oxidative damage (Ganesan and Xu 2018). According to this study, it was found that certain mushroom species contain compounds that modulate inflammatory signaling pathways, such as NF-κB and Toll-like receptors (TLRs). By suppressing excessive microglial activation and the production of neurotoxic mediators, these mushroom extracts can exert neuroprotective effects. This dual mechanism against oxidative stress and inflammation provides a sturdy biochemical basis for their potential cognitive benefits (Musella et al. 2018; Vaidya and Mandalika 2015; Pan et al. 2018; Lee et al. 2018).

- Neurotransmitter System Interactions:

While research is less extensive in this area compared to neurotrophic factors and inflammation, some studies have shown medicinal mushrooms may interact with various neurotransmitter systems. For example, certain mushroom compounds might influence the synthesis or metabolism of acetylcholine, a neurotransmitter crucial for memory and learning. Other potential interactions could include modulating dopaminergic or serotonergic pathways, which are involved in mood and executive functions. While direct evidence linking these specific compounds to widespread cognitive enhancement through neurotransmitter modulation is still under development, the potential for these interactions to exist leads us to further investigation (Zhang et al. 2016).

4.4 Physiological Impact on Brain Health

Beyond their well-documented biochemical properties, these medicinal mushrooms exert a significant influence on several key physiological systems that help to maintain essential and optimal brain health and cognitive function. These effects span from neuroplasticity, energy metabolism, and the gut-brain axis, which are the three main interconnected domains critical for brain resilience and performance.

- Neuronal Plasticity and Synaptic Function

The brain's capacity for change is known as neuroplasticity, which is essential for learning, memory formation, and recovery from neuronal injury (Fischer-Baum and Campana 2017). This also includes synaptic plasticity, strengthening or weakening connections between neurons, and neurogenesis, particularly in the hippocampus region. The influence of some mushrooms on neurotrophic factors can directly contribute to enhanced neuroplasticity (Kim et al. 2020). These mushroom

compounds physiologically reinforce the brain's foundational structures for cognitive processes (Pan et al. 2018) by promoting neuron survival, growth, and differentiation, and supporting synapse formation and maintenance. This physiological support for the neuroplastic mechanism is considered a key way for medicinal mushrooms to contribute to cognitive enhancement and resilience against age-related decline.

- Cerebral Blood Flow and Energy Metabolism

The brain is an energy-demanding organ that relies on a constant supply of oxygen and glucose, which are delivered via cerebral blood flow. Efficient energy metabolism within neurons and glial cells is crucial for maintaining neural activity and preventing cognitive fatigue. Some medicinal mushrooms, such as *Cordyceps*, are associated with increased energy and reduced fatigue (Geng et al. 2017). Extracts from *Cordyceps sinensis* and *Cordyceps militaris* have been shown to increase oxygen uptake and also increase circulation in both animal and human models. Studies document improvements in VO_2 max and blood oxygen saturation, which suggests enhanced oxygen delivery to brain tissue during physical or mental exertion (Chen et al. 2010; Lee et al. 2006).

- Gut–Brain Axis Connection

The gut–brain axis (GBA) is a complex, bidirectional communication system that links the CNS with the enteric nervous system (ENS), connecting the emotional and cognitive centers of the brain with peripheral intestinal functions. Disruption of this communication system can affect in various ways, leading to neuropsychiatric and neurodegenerative disorders, which include anxiety, depression, autism spectrum disorder, and Alzheimer's disease (Cryan et al. 2019).

Recent evidence suggests that medicinal mushrooms can influence this gut–brain interaction through their prebiotic, anti-inflammatory, and immunomodulatory properties. *G. lucidum* (Reishi), *L. edodes* (Shiitake), and *Grifola frondos*a (Maitake) have abundant beta-glucans and other polysaccharides that serve as substrates for beneficial gut microbes.

These polysaccharides promote the growth of various health-associated bacteria such as *Lactobacillus* and *Bifidobacterium*, leading to improved gut barrier integrity and production of neuroactive metabolites like short-chain fatty acids (SCFAs), which play a pivotal role in maintaining the integrity of the blood–brain barrier, modulating neuroinflammation, and influencing the expression of brain-derived neurotrophic factor (BDNF) (Li et al. 2018a, b; Silva et al. 2020).

4.5 Key Medicinal Mushrooms for Cognitive Support

- Lion's Mane (*Hericium erinaceus*)

Lion's Mane is perhaps the most widely studied medicinal mushroom for its direct effects on cognitive health. Its fruiting body and mycelium contain compounds known as hericenones and erinacines, respectively (Li et al. 2018a, b). These compounds are notable for their ability to stimulate the synthesis of nerve growth

factor (NGF), which is crucial for the growth, maintenance, and survival of neurons, particularly cholinergic neurons, which are involved in memory and learning (Wong et al. 2012).

Experimental studies in rodents have consistently proven to show the cognitive benefits of *H. erinaceus*. For instance, a study conducted in mice that were administered Lion's mane extract exhibited improved performance and enhanced recognition. These results were attributed to not only the elevated levels of NGF but also the mushroom's anti-inflammatory and antioxidant actions, which help to mitigate neurodegeneration and oxidative stress, key contributors to cognitive decline and disorders such as Alzheimer's disease (Friedman 2015).

- Reishi (*Ganoderma lucidum*)

G. lucidum, commonly known as Reishi or Lingzhi, is a medicinal mushroom used in traditional Chinese medicine for its health-alleviating properties. Often referred to as the "plant of immortality," it can also be used for the body to cope with stress.

While its direct impact on neurotrophic factors is less focused than Lion's Mane, Reishi is rich in triterpenoids and polysaccharides that possess potent antioxidant and anti-inflammatory properties (Bulam et al. 2019). Polysaccharides extracted from Reishi have been shown to promote neural progenitor cell proliferation and help to improve cognitive deficits seen in Alzheimer's disease (AD) mouse models. This effect is mediated via the activation of Fibroblast Growth Factor Receptor 1 (FGFR1) and downstream activity of extracellular signal-regulated kinase (ERK) and AKT signaling pathways (Huang et al. 2017). Reishi polysaccharides also exhibit anti-inflammatory activity by modulating the gut–brain axis. Certain mouse models were subjected to high-fat diets and chronic stress. In these polysaccharides, improved cognitive functions were observed because of the inhibition of NLRP3/NF-κB signaling pathways and the alteration of gut microbiota composition (Jiang et al. 2025).

- *Cordyceps* (*Cordyceps* spp.)

Cordyceps species, particularly *C. sinensis* and *C. militaris*, are traditionally used to combat fatigue, increase energy levels, and improve endurance. *Cordyceps* is thought to improve cellular energy production, potentially by enhancing ATP synthesis and oxygen utilization. Reducing fatigue can indirectly improve alertness, concentration, and overall mental performance. The antifatigue effects of *Cordyceps* are linked to various bioactive constituents, including polysaccharides, peptides, and nucleosides (Geng et al. 2017). Oxidative stress was seen to be a major contributor to the decrease in cognitive function and neurodegeneration. *Cordyceps* extracts have shown strong antioxidant properties that protect neurons from reactive oxygen species (ROS)-induced damage. Studies in the past have shown that *C. sinensis* extracts reduce levels of malondialdehyde and increase superoxide dismutase activity in brain tissue (Zhu et al. 1998).

4.6 Current Research Landscape and Future Perspectives

The scientific investigation into the cognitive effects of medicinal mushrooms is an expanding field that bridges traditional knowledge with modern pharmacological advancements.

Current researches are primarily conducted in vitro settings and animal models, providing valuable insights into the potential biochemical and physiological mechanisms underlying these effects, such as neurotrophic factor modulation, antioxidant defense, and anti-inflammatory actions. Most studies have been performed in animal models, and more human trials are necessary to verify the antifatigue and cognitive functions of edible and medicinal mushrooms (Lee et al. 2018; Geng et al. 2017). Human trials conducted so far are often limited by small sample sizes, short durations, variations in mushroom species and preparation methods (e.g., extracts, whole powder, mycelium vs. fruiting body), and a lack of standardized dosing. Establishing an optimal dosage rate and understanding its potential interactions with medications and specific populations are most likely to benefit, require thorough clinical investigation.

4.7 Conclusion

Medicinal mushrooms represent and hold a compelling frontier in the pursuit of cognitive health, while combining centuries' worth of traditional usage with mounting modern scientific evidence. Because of their diverse bioactive compounds, key species like *G. lucidum*, *H. erinaceus*, and *Cordyceps* spp. have all shown promising roles in enhancing memory and neuroplasticity, regulating energy metabolism, and modulating the brain axis. While preclinical studies provide encouraging data and therapeutic potential, this field remains in its infancy, with several challenges ahead.

Future research must prioritize large-scale human trials with standardized mushroom preparations to better understand the dosage, safety, long-term outcomes, and clinical relevance across different cognitive conditions. Interdisciplinary collaboration between neuroscientists, mycologists, clinicians, and pharmacologists will be essential to translate these natural compounds into evidence-based interventions. As the global burden of neurodegenerative diseases continues to rise, these medicinal mushrooms may emerge as safe, accessible, and multifaceted tools to preserve cognitive health and improve quality of life, particularly in aging populations.

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5 Molecular Basis and Potential Antioxidant Mechanisms of Medicinal Mushrooms

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Abstract

Medicinal mushrooms, as a rich source of health-promoting compounds, have been at the center of much research over the last decades. Immunomodulatory, antioxidant activity, antitumor, neuroprotection, and antiaging effects are among the important attributes of these mushrooms. Their significant results on health are due to various types of components, especially bioactive compounds, including polysaccharides, ergothioneine, polyphenols, flavonoids, carotenoids, lectins, and terpenoids, which make their impact through different molecular basis and mechanisms of action. The antioxidant activity of these compounds is exerted by both direct and indirect antioxidant pathways. Direct pathways are carried out via scavenging reactive oxygen species and chelating of pro-oxidant metals, preventing Fenton reactions and cellular damage. In indirect pathways, they modulate endogenous antioxidant defenses by upregulating essential antioxidant enzymes. This chapter aims to provide an inclusive review of molecular

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mechanisms of medicinal mushrooms' components, in which they exhibit beneficial impacts on health, especially their antioxidant activity.

Keywords

Medicinal mushrooms · Antioxidant mechanisms · Oxidative stress · Bioactive compounds

5.1 Introduction

ATP production and energy metabolism in all aerobic organisms depend on oxidation (Yang et al. 2002). During oxidation and cellular aerobic metabolism, reactive oxygen species (ROS) and free radicals are naturally generated in mitochondrial respiration. External factors, including UV radiation, drug metabolism, and stress, can also generate ROS. (Juan et al. 2021). ROS such as superoxide anion ($O_2^{\bullet -}$), hydroxyl radical (OH•), hydroxyl ion (OH−), nitric oxide (NO•), and hydrogen peroxide (H2O2) are produced in small amounts in normal physiological conditions and are neutralized by defense antioxidant enzymes in human bodies. Trace metals, including iron (Fe), copper (Cu), and magnesium (Mg), can participate in the Fenton reaction, a chemical process in which metal ions react with hydrogen peroxide (H_2O_2), generating free radicals (Arunachalam et al. 2022; Sánchez 2017).

An upsurge of ROS and an imbalance between ROS and natural antioxidant enzymes leads to excessive ROS accumulation. Excessive ROS, known as oxidative stress, is highly harmful to the body. It can damage nucleic acid, oxidize proteins, and initiate lipid peroxidation. These mechanisms result in cell apoptosis and accelerate the aging process (Sánchez 2017). Therefore, oxidative stress is responsible for the development of numerous diseases. Neurodegenerative diseases such as amyotrophic lateral sclerosis, Alzheimer's, and Parkinson's, cardiovascular disorders including hypertension, atherosclerosis, and other severe conditions, such as cancer, are all associated with oxidative stress (Pizzino et al. 2017). Although oxidative stress can damage all organs, the brain is more vulnerable due to its high oxygen demand and high concentration of polyunsaturated fatty acids. Not all brain neurons are equally tolerant to oxidative stress; neurons in specific regions, such as the hippocampal CA1 region and the cerebellar granule cell layer, are more susceptible to oxidative stress (Trofin et al. 2025; Wang and Michaelis 2010). To deactivate the oxidative stress damage, organisms rely on antioxidant enzyme defenses in the body. In normal physiological conditions, where ROS production is not excessive, antioxidant enzymes rapidly detoxify ROS. Superoxide dismutase (SOD) transited ROS to hydrogen peroxide (H2O2) and then glutathione peroxidase (GPx) converts H2O2 to H2O and O2 within the mitochondria. H2O2 can also diffuse to the cytosol and be neutralized by catalase (CAT) enzymes in the peroxisomes (Evans et al. 2002). However, in conditions of sustained oxidative stress, the body's capacity to counteract excessive ROS is inadequate. Natural products containing high

concentrations of antioxidants, such as vegetables and fruits, can boost the body's capacity to scavenge free radicals (Cheung et al. 2003).

Medicinal mushrooms are a valuable source of vitamins, including vitamin B1, B2, B12, C, D, E, and minerals such as manganese, iron, calcium, potassium, magnesium, zinc, selenium, and phosphorus. They are also rich in natural antioxidants and can enhance the body's antioxidative defense enzymes through diet. Mushrooms possess precious bioactive compounds such as polysaccharides, ergothioneine, polyphenols, flavonoids, carotenoids, lectins, and terpenoids. Bioactive compounds in mushrooms contribute to several antioxidant effects by scavenging free radicals, enhancing endogenous antioxidant enzymes, and chelating metal ions that catalyze free radicals (Kozarski et al. 2015; Grazia Maria Liuzzi et al. 2023). In this chapter, we aim to provide a comprehensive review of the molecular basis and potential antioxidant mechanisms of medicinal mushrooms with a special focus on their impacts on the nervous system.

5.2 Antioxidant Pathways

Mushroom bioactive compounds exhibit their antioxidant effects through direct and indirect pathways. These compounds represent indirect antioxidant activity by boosting prominent defense antioxidant enzymes, including SOD, CAT, and GSH-Px, and therefore prevent oxidative damage to cells (Lu et al. 2020; Zhang et al. 2016a). One of their direct mechanisms is free radical scavenging. They donate hydrogen atoms or electrons to ROS and neutralize free radicals by converting them into more stable and nonreactive molecules. This process helps prevent oxidative stress damage to cellular components (Karuppusamy Arunachalam et al. 2022; Bamigboye et al. 2021). Metal ion chelation represents another direct antioxidant effect of mushrooms. Hydroxyl and carboxyl groups in mushroom compounds can bind to metal ions such as ferrous iron (Fe^{2+}) and copper (Cu^{2+}), preventing these ions from participating in the Fenton reaction. Chelating trace metals can reduce the generation of additional free radicals and mitigate oxidative stress effects (Singh et al. 2025; Wang et al. 2015).

Bioactive components in mushrooms, such as polysaccharides and phenolic compounds, also exert direct antioxidant effects by inhibiting lipid peroxidation. Lipid peroxidation is a three-phase process consisting of initiation, propagation, and termination. The initiation phase occurs when a free radical attacks a lipid molecule, primarily a polyunsaturated fatty acid, and abstracts a hydrogen atom from the lipid structure. This phase forms a lipid radical (L-) and an alkoxyl (LOS•). During the propagation phase, the lipid radical (L-) reacts with an oxygen molecule and forms a peroxyl radical (LOO-). The chain reaction of lipid peroxidation is initiated by generating a peroxyl radical (LOO-). The peroxyl radical (LOO·) persistently targets adjacent lipids, resulting in the formation of hydroperoxides (LOOH). Lipid peroxidation is a self-propagating process that continues until it leads to cellular damage. The chain reaction terminates when antioxidants such as mushroom bioactive components donate hydrogen atoms to lipid radicals and neutralize them. This

reaction can prevent additional lipid damage (Nam 2011; Sun et al. 2004). Malondialdehyde (MDA) is a biomarker formed as a byproduct of lipid peroxidation and is used to measure oxidative stress in various diseases (Cordiano et al. 2023). Mushroom bioactive compounds can prevent lipid peroxidation by chelating metals, interrupting the Fenton reaction, and lowering the generation of hydroxyl radicals that initiate lipid peroxidation (Liu et al. 2017). Additionally, they can directly scavenge reactive species, such as hydroxyl and lipid radicals, terminating the chain reaction (Sun et al. 2004).

5.3 Polysaccharides

Polysaccharides are the most significant antioxidant compounds in medicinal mushrooms. Both homopolysaccharides and heteropolysaccharides are present in medicinal mushrooms. Mushroom polysaccharides differ from other polysaccharides, primarily containing β-glucan, D-glucan, or a mixed glucan. β-glucans are homopolysaccharides, and their main chain consists of β-(1→3) linkages with some β-(1→6) branches. β-glucan is a key contributor to the antioxidant effect in medicinal mushrooms and plays an important role in the fungal cell wall. Mushroom polysaccharides, primarily β-glucan, exhibit antioxidant effects by scavenging ROS, inhibiting lipid peroxidation, and ion chelation (Chun et al. 2021; Grazia Maria Liuzzi et al. 2023). The main antioxidant effect of β-glucan is mediated through upregulating the expression of endogenous antioxidant enzymes such as SOD, CAT, and GSH-Px. This upregulation is mediated by Nuclear Factor erythroid 2-related factor 2 (Nrf2) activation. Nrf2 is a transcription factor and a major element for antioxidant enzyme production (Yang et al. 2025). Under normal conditions, Nrf2 binds to its inhibitor, Kelch-like epichlorohydrin-associated protein-1 (Keap1), which is located in the cytoplasm. During oxidative stress and free radicals' presence, Nrf2 detaches from Keap1 in the cytoplasm. Free Nrf2 rapidly translocates into the nucleus. Nrf2 binds to small musculoaponeurotic fibrosarcoma oncogene homolog (sMaf) protein and forms a heterodimer that binds its target DNA regions. This dimer binds to antioxidant response elements (AREs) in DNA, promoting the expression of genes responsible for antioxidant defense enzymes such as SOD, CAT, and GSH-Px, which enhances their cellular levels (Luo et al. 2023; Xia et al. 2022). Polysaccharides in mushrooms activate this pathway by enhancing the expression of phosphatidylinositol 3-kinase (PI3K) and the phosphorylation of protein kinase B (AKT) (Xia et al. 2022). PI3K and AKT are crucial for Nrf2 activation and stabilization, and the PI3K/Akt pathway can regulate the Nrf2-ARE pathway (Wang et al. 2008).

β-glucan possesses immunomodulatory and antitumor effects as well. It can bind to immune cell receptors such as the Dectin-1 receptor, complement receptor 3 (CR3), and toll-like receptors (TLRs) due to its β- (1→3) backbone and β- (1→6) branches. The Dectin-1 receptor and CR3 are widely expressed on macrophages, dendritic cells, and neutrophils. Therefore, β-glucans can stimulate the activation of macrophages, natural killer cells, and T lymphocytes while enhancing

phagocytosis. Additionally, β-glucan can interact with Toll-like receptors (TLRs), transmembrane receptors that detect microbial components, and also activate these receptors synergistically, thereby improving the immune defense system (Kim et al. 2011).

5.4 Polyphenols

Polyphenols are another natural antioxidant bioactive molecule in medicinal mushrooms. Polyphenols have at least one hydroxy group attached to an aromatic ring in their structure (Oesterle et al. 2024). Polyphenols offer protection from ultraviolet radiation and pathogens due to their structure. Based on the number of phenolic rings and their structural characteristics, these bioactive components can be categorized into several groups, such as flavonoids, phenolic acids, stilbenes, and lignans (Grazia Maria Liuzzi et al. 2023). Mushroom polyphenolic compounds can participate in the redox cycling by donating hydrogen atoms or electrons. This way, polyphenols can effectively contribute to free radical scavenging and ion chelating. Moreover, they can upregulate endogenous antioxidant enzymes by activating the Nrf/ARE signaling pathway, directly affecting the dissociation between Nrf2 and Keap1 (Kozarski et al. 2015; Xia et al. 2022).

The main polyphenolic component in mushrooms is phenolic acids, and they can be divided into two major subgroups: hydroxybenzoic and hydroxycinnamic. These compounds have potential antioxidant properties related to various health benefits, including anti-inflammatory, antiaging, and neuroprotection (Kozarski et al. 2015) Chu et al. reported significant antioxidant activity of phenolic compounds in mushrooms, primarily due to their strong ability to donate hydrogen atoms and detoxify free radicals. Mushrooms are a rich source of diverse phenolic compounds, which can contribute to health benefits (Chu et al. 2023).

Flavonoids are the most studied group among polyphenols. Their structure features a flavone nucleus made up of a 15-carbon atom skeleton. This includes a C6-C3-C6 framework with two benzene rings, called rings A and B. These rings are linked by a bridge of three carbon atoms that creates a heterocyclic pyran ring, known as ring C, which contains an oxygen atom (Dias et al. 2021; Grazia Maria Liuzzi et al. 2023). Flavonoids protect cells against oxidative stress damage via several mechanisms. The arrangement, especially the quantity and placement of hydroxyl groups and conjugated double bonds, allows flavonoids to neutralize reactive species effectively. This results in enhanced antioxidant activity of flavonoids. The optimal condition for neutralizing free radicals arises when their structure features a hydroxy group at the 4′ and 3′ positions of the B ring, a conjugated double bond between carbons 2 and 3, an oxo group at the 4 position of the C ring, a hydroxy group on carbon 3 of the C ring, and a hydroxy group on carbon 5 of the A ring (Hassanpour and Doroudi 2023). They can inhibit enzymes, which produce free radicals as well, such as xanthine oxidase and lipoxygenase (Fiorucci et al. 2008; Lin et al. 2015). Xanthine oxidase is an enzyme that contributes to purine oxidation. It can generate free radicals such as superoxide and hydrogen peroxide.

The molybdopterin molecule is the cofactor at the active site of xanthine oxidase, which is located in the enzyme cavity and has catalytic activity (Lin et al. 2015).

Flavonoids can inhibit xanthine oxidase through their specific structure. Due to their C2═C3 double bonds, flavonoids can bind to the xanthine oxidase enzyme's cavity and interact with the molybdopterin cofactor. They can inhibit this enzyme by occupying its active site and preventing the generation of excessive ROS (Lin et al. 2015). Lipoxygenases (LOXs) are peroxidizing enzymes because they can dioxygenate (adding oxygen to lipids) primarily polyunsaturated fatty acids (PUFAs) such as linoleic acid and arachidonic acid. This leads to the production of hydroperoxides (Fiorucci et al. 2008; Mashima and Okuyama 2015), which are unstable molecules, can react with alkoxy radicals (RO), and generate free radicals. Particularly in the presence of trace metals such as copper or iron, these reactions are more emphasized (Salem et al. 2000; Vereecken et al. 2004). Hydroperoxides are precursors of inflammatory mediators such as leukotrienes and lipoxins. Therefore, hydroperoxides are pro-inflammatory and pro-oxidant substances. Due to the role of hydroperoxides in inflammation and oxidative stress, LOXs are associated with various diseases. Flavonoids can inhibit LOXs by directly binding to the active site of the LOX enzyme and preventing them from reacting as peroxidizing enzymes (Fiorucci et al. 2008; Sroka et al. 2017). Flavonoids, such as quercetin, exert their antioxidant activity by donating a hydrogen atom from their hydroxyl group to metal ions and chelating them (Bolaño Alvarez et al. 2024).

5.5 Ergothioneine

Ergothioneine is a sulfur-containing bioactive compound found in mushrooms and serves as a natural potent antioxidant in foods. Among all foods, mushrooms contain the highest levels of ergothioneine (Apparoo et al. 2024). The human body cannot produce ergothioneine and can only uptake it through diet. Fungi and some bacteria can synthesize ergothioneine. SLC22A4 is an ergothioneine-specific transporter in humans that helps ergothioneine accumulate in tissues that are more sensitive to oxidative stress, such as bone marrow, liver, kidney, seminal fluid, and the lens and cornea of the eyes (Borodina et al. 2020). Ergothioneine is highly stable under heat, different pH ranges, and light (Liu et al. 2020) and is related to cell glutathione levels. Glutathione is another sulfur-containing antioxidant and one of the primary antioxidant defense enzymes in the body. Due to glutathione's ability to neutralize free radicals, it has significant implications for preventing various diseases (Kalaras et al. 2017). Ergothioneine and glutathione act synergistically and participate in the GSH/glutathione disulfide (GSSG) redox couple. After ergothioneine neutralizes free radicals and becomes oxidized, GSH reduces the oxidation of ergothioneine and returns ergothioneine to its active form. This process makes ergothioneine a potent radical scavenger without depleting (Liu et al. 2023). Ergothioneine can also upregulate antioxidant defense enzymes by Nrf2/ARE pathway activation and enhance antioxidant enzymes in the body (Fu and Shen 2022; Liu et al. 2023). Ergothioneine can directly interact with Nrf2, upregulating the Nrf2/ARE pathway.

Evidence indicates that ergothioneine can bind to KEAP1, accumulate Nrf2 in the nucleus, and enhance endogenous antioxidant enzyme expression. It also enhances PI3K, serine/threonine kinase, and protein kinase C (PKC). Since these factors can activate Nrf2, they indirectly stimulate the Nrf2/ARE pathway (Chen et al. 2024a). Ergothioneine can chelate numerous metal ions, including Fe, Cu, zinc (Zn), nickel (Ni), and cobalt (Co), preventing them from participating in the Fenton reaction and generating reactive species (Fu and Shen 2022).

5.6 Lectins

Lectins, as an important component of mushrooms, have been reported to have various therapeutic properties. Based on structural attributes, they can be classified into seven groups: calnexin, L-type, P-type, C-type, galectins, I-type, and R-type. The first three are intracellular, while the latter are extracellular (Singh et al. 2020). Due to their biological functions, lectins have been one of the main focuses of many studies in recent years, revealing their different effects, such as antiproliferative and antitumor activities toward tumor cells, hypotensive activity, and immunomodulatory effects. As a result of its lectin–carbohydrate interactions, lectin plays a significant role in different cellular functions like adhesion, growth, morphogenesis, molecular recognition, and pathogenesis (Singh et al. 2015). An example of lectin–carbohydrate interactions is lectins' binding to glycosylated receptors on the cell surface, which activates signaling pathways. Another example is lectin's binding to GluN1/GluN3A and GluN1/GluN3B receptors involved in excitatory neurotransmission that have been shown to be modified and impacting the central nervous system. Through a single N-glycosylation site on the GluN3 subunit, this modification occurs, so lectin can act as a means to impact disorders like Huntington's disease associated with altered expression of GluN3 subunits (Singh et al. 2020). One possible explanation is that through reduction in desensitization of GluN3-containing N-methyl-D-aspartate receptors (NMDARs), intracellular Ca2+ signaling, and/or neuronal survival could be modified by lectins, which may exhibit significant functional outcome in both normal and pathological conditions (Hemelikova et al. 2019). For example, a rise in extracellular concentrations of glutamate is caused by the increase in NMDARs stimulation, which leads to neuronal injuries (Murai et al. 2022; Paoletti et al. 2013). Research has shown that excitotoxicity is induced by the increase in Aβ- and tau production, and also their changes in synaptic plasticity and synapse loss are intervened by GluN2B-containing NMDARs' stimulation. All of those conditions lead to various central nervous system (CNS) disorders (Paoletti et al. 2013).

The anti-inflammatory and antioxidant effects of the lectins occur due to their binding to glycoproteins and glycolipids that exist on immune cells, such as macrophages, dendritic cells, and T cells, which can provoke cellular activation and inflammatory responses. This results in the production and release of pro-inflammatory cytokines. On the other hand, lectins elevate anti-inflammatory cytokines like IL-10 and TGF-β that impede the production of pro-inflammatory

cytokines, therefore creating a balanced immunomodulation impact (Konozy and Osman 2024). Additionally, lectins can act as direct defense factors by neutralizing antagonists upon binding and enhancing the immune system's recognition of pathogens (Singh et al. 2015).

5.7 Terpenoids

Terpenoids or isoprenoids are a type of terpenes derivative that contain attached elements or functional groups that are synthesized by microbes, fungi, plants, and animals (Perveen and Al-Taweel 2018). Terpenoids exist in different forms, such as monoterpenes, sesquiterpenoids, diterpenoids, triterpenes, and polyterpenoids, which contain by order two, three, four, six, and more than eight isoprene units (Smanski et al. 2012). Many studies have reported anti-inflammatory effects of terpenoids, which are mainly implemented via mechanisms involved in inhibiting pro-inflammatory cytokine expression, intracellular and extracellular signaling pathways' regulation, and the repression of protein kinases implicated in inflammatory processes (Trepa et al. 2024). As mentioned, terpenoids exhibit anti-inflammatory impacts by reducing pro-inflammatory cytokines (including IL-1β, IL-6, and TNF-α) and nitric oxide (Zhang et al. 2021). Since terpenoids can pass across the blood–brain barrier, it is indicated that they can be efficient against neurodegenerative diseases by their neurotropic factors (Dasgupta and Acharya 2019).

The PI3K/Akt pathway is a crucial signaling pathway of the nervous system involved in modulating neuronal growth, proliferation, survival, and function. Previous studies show terpenoids regulate the PI3K/Akt pathway, resulting in a neuroprotective impact. Akt phosphorylation derived from P13 activation targets proteins related to metabolism and anti-apoptosis pathways, therefore controls cellular mechanisms. Akt activation enhances cell survival by inducing nuclear translocation of Nrf2 and p-CREB, leading to an elevation in expression of antioxidant and neuroprotective genes like heme oxygenase-1. In addition, Akt impacts protein synthesis, apoptosis, and neuronal activity by altering gene expression of mTOR, GSK-3β, Bax, and Bcl-2 (Câmara et al. 2024; Xu et al. 2022).

Cyathane diterpenoids interfere with the TrkA-NGF receptor-ligand complex, which leads to the regulation of the activating impacts of NGF and function as a neuroprotective element (Jin et al. 2016). As a member of the cyathane diterpenoids' family, Erinacine A exhibited a significant impact on the nervous system through a multifactorial mechanism and different molecular pathways. Erinacine A can reduce proteins with nitrotyrosine, phosphorylation of p38 MAPK (mitogen-activated protein kinase) and CCAAT enhancer-binding protein (C/EBP), and homologous protein (CHOP). Therefore, it inhibits neuron death and elevates nerve-growth factor amounts (Thongbai et al. 2015).

Furthermore, it is shown that erinacine A modulates the generation of ROSs, malondialdehyde, nitric oxide, and superoxide dismutase, and as a result, represses the oxidative stress in the body (Qin et al. 2016). In addition to pro-inflammatory cytokines and reactive nitrogen species, erinacine A has been reported to

downregulate gene expression involved in ischemic conditions like inducible NO synthase (iNOS), p38/MAPK, and CHOP (Lee et al. 2014). Another natural cyathane diterpene, 11-O-acetylcyathatriol, has been shown to initiate the MAPK/p38 transduction pathway, which can evoke responses like cellular proliferation, differentiation, inflammatory responses, and apoptosis, and is linked to suppression of COX-2 proteins and iNOS (Jin et al. 2016).

5.8 *Coriolus versicolor*

Coriolus versicolor (CV) is endemically found in China and has been used as a medicinal food for centuries (Jing et al. 2022). It is called *Yun zhin* in China, North America as Turkey tail, and Japan as Kawaratake. The main bioactive compound is polysaccharopeptides (PSP), which can be extracted mainly using boiling water, with the help of ultrasonic waves and enzymes (Gong et al. 2020). CV has two prominent bioactive substances, COV-1 (PSP) and polysaccharide krestin (PSK) (Saleh et al. 2017). Furthermore, the structure of polysaccharides impacts the function; for instance, the number of monosaccharides and the weight of the molecule affect the antioxidant capability (Pattanayak et al. 2015). Antioxidant function is brought by the ability of polysaccharides to bind with hydroxyl radicals, reactive oxygen species (ROS), and superoxide anion to form water (Fang et al. 2015). Other radicals scavenged by the polysaccharides are 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical, and 2,20-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical (Sun et al. 2014). Additionally, higher concentrations of glucuronic acid molecules in acidic polysaccharides and higher glucose content in neutral polysaccharides correlated with greater antioxidant activity (Maity et al. 2021). Besides, upregulating the enzymes responsible for antioxidant ability such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), and lowering the amount of MDA is another mechanism by which antioxidant activity is undertaken (Chen et al. 2013).

In Alzheimer's disease rat models, CV improves spatial memory through the antioxidant mechanism (Fang et al. 2015). Furthermore, it also increases the levels of substances that are released during stress response, such as lipoxin A4, which is an anti-inflammatory mediator, heat shock protein 70 (Hsp70), thioredoxin (Trx), and heme oxygenase 1 (HO-1) in the hippocampus and cortex (Trovato et al. 2016). In neurodegenerative diseases, neuroinflammation is marked by the rise of Glial Fibrillary Acidic Protein (GFAP), Ionized Calcium-Binding Adapter Molecule 1 (Iba-1), and the degradation of Inhibitor of Nuclear Factor Kappa-B Alpha (Ikb-α) (Impellizzeri et al. 2016). On the other hand, traumatic brain injury (TBI) triggers inflammation through the Nuclear Factor kappa B (NF-κB) pathway, leading to ROS production (Gaetz 2004). Moreover, α-synuclein (α-syn) accumulates, and a decrease in tyrosine hydroxylase (TH) and dopamine transporter (DAT) markers is noted along with the markers of cell death, such as Bcl-2-associated X protein (Bax) and B-cell lymphoma 2 (Bcl-2) (Phani et al. 2012). CV has contributed to a decrease in α-syn levels, an increase in antiapoptotic Bcl-2, and a decrease in pro-apoptotic

Bax. In addition, dopaminergic neuronal death drop was observed with the rise of TH and DAT, which are markers of dopaminergic neurons (Cordaro et al. 2022). CV upregulates the antioxidant molecules such as Nuclear Factor erythroid 2-related factor 2 (Nrf-2), HO-1, Hsp-70, γ-Glutamylcysteines (γGCs), and Trx, thus decreasing the oxidative stress within brain cells in the regions of cerebellum, cortex, and hippocampus. Hence, CV acts on the NF-κB pathway, astrocytes, and microglia, decreasing neuroinflammation (D'Amico et al. 2021). In sum, CV decreases oxidative stress, accumulation of α-syn, neuroinflammation, and the death of dopaminergic neurons, making it a good neuroprotective food.

5.9 *Ganoderma Lucidum*

For centuries, *Ganoderma Lucidum* (GL) has been a traditional Chinese food that has medicinal properties (Ren et al. 2022). It is known as Lingzhi in China, Reishi in Japan, and Mannentake in Korea, and is believed to increase life span (El Sheikha 2022). Out of many bioactive compounds, the main vital substances are polysaccharides and triterpenoids (Sharif Swallah et al. 2023). Glucans, β-1-3 and β-1-6 D glucan, are the main polysaccharides extracted from GL, and these molecules enhance the immune system (Sharma et al. 2019). Meanwhile, triterpenoids such as ganoderic acids (GA) tend to decrease neuroinflammation (Sheng et al. 2019). Strong antioxidant activity attributed to phenolics, carotenoids, flavonoids, and other organic acids, which are found in GL, is shown (Erbiai et al. 2023). Another study revealed that the activity of catalase and superoxide dismutase was increased when extracts of GL were used, thus removing reactive oxygen species (ROS) (Smina et al. 2011).

In brain health, a study conducted to evaluate the effectiveness of GL on decreasing the hydrogen peroxide or the damage caused by β-amyloid in neuroblastoma cells revealed increased cell viability (Huang et al. 2024). The polysaccharides take over the antioxidant responsibility, which scavenge free radicals and boost the activity of antioxidant enzymes. Furthermore, the lower the molecular weight of polysaccharides, the greater the antioxidant activity, and other antioxidant mechanisms include metal chelation and decreased lipid peroxidation (Ahmad et al. 2024). Moreover, the three-helix structure of polysaccharides provides a unique interaction and properties of GL (Lian et al. 2024). Anti-inflammatory function is unveiled by experiments that confirmed a decrease in TNF-α, IL-6, IL-1β, NO, and other inflammatory mediators by stopping the MAPK signaling route, which is induced by LPS. In addition, oxidative stress was mitigated by triggering the Nrf2/Keap1 signaling pathway (Hu et al. 2020). Spinal cord injury tested in rats revealed that the β-D-glucan component of the polysaccharide decreased the apoptosis factors, such as caspase-3, and inflammatory factors (Gokce et al. 2015).

Triterpenoids also exhibited antioxidant activity against hydroxide, DPPH, and ABTS (2,2′-Azinobis-(3-ethylbenzthiazoline-6-sulfonate)) free radicals (Huang et al. 2022). Additionally, peptides released from enzymatic hydrolysis lowered oxidative stress (Aursuwanna et al. 2022). Moreover, *G. lucidum* protease hydrolysate

(GLPH) from stomach enzymes influences the gut–brain axis by reducing triglycerides, low-density lipoprotein, and total cholesterol and modifying the intestinal flora by decreasing harmful bacteria (Xiong et al. 2022).

In Alzheimer's disease (AD), it is found that GL neutralizes the Aβ amyloid peptide neurotoxicity. Moreover, synaptotoxicity induced by Aβ is counteracted by upregulating synaptophysin levels, and apoptosis reduction is observed with decreased caspase-3 like action and apoptotic bodies by weakening stress kinases (Chen et al. 2024b). Triterpenoids preserved hippocampal integrity and decreased the neurofibrillary tangles formed from tau protein hyperphosphorylation. Furthermore, anti-apoptotic function and antioxidant activity by the triterpenoids are achieved by inhibiting the ROCK signaling route (Yu et al. 2020). Overexpression of Microtubule affinity regulation kinase 4 (MARK4) is observed in the beginning of AD and Parkinson's disease (PD), and in the study conducted to find the inhibitors of MARK4, ganoderenic acid A (GAA) and ganoderenic acid B (GAB) diminished the phosphorylation of tau protein by binding to MARK4 (Ahmad et al. 2023). Besides, autophagy in microglial cells is enhanced by GAA via promoting Axl phosphorylation, thus clearing $A\beta_{42}$ from the cells (Qi et al. 2021). In addition, the decline in neuroinflammation is understood from the diminished levels of pro-inflammatory cytokines (Cai et al. 2017; Sheng et al. 2019). Nerve growth factor mimicking activity by GL extracts was observed in a study (Ling-Sing Seow et al. 2013).

Sleep disturbance leads to neuroinflammation by microglial activation and consequent inflammatory cascade (Irwin and Vitiello 2019). Moreover, GL modulates two key pathways in the medial prefrontal cortex: the Brain-Derived Neurotrophic Factor (BDNF)/Tropomyosin Receptor Kinase B (TrkB) signaling pathway and the NF-κB/NOD-like Receptor Family Pyrin Domain Containing 3 (NLRP3) pathway, and also enhances GABAergic signaling in the parabrachial nucleus. Hence, sleep disturbances are alleviated by these mechanisms (Qin et al. 2024).

In a study conducted on mice, anxiety and depression induce inflammation from microglia, which then contributes to neuroinflammation, but administration of GL significantly rectified this without any recorded toxicities (Mi et al. 2022). Thus, GL has been shown to have numerous properties, including neuroprotection, antioxidant, and anti-inflammatory effects on brain well-being.

5.10 *Pleurotus spp.*

Pleurotus spp is the mushroom that is most popular in China and known as "white rot fungi" (Tsujiyama and Ueno 2013). *Pleurotus giganteus* has been present in villages across the Malaysian peninsula, widely known as "*Seri Pagi*," meaning morning glory, and in China, it's called "Zhudugu," meaning stomach (Phan et al. 2012). Its immunomodulatory function and antioxidant capability are noted, which help to reduce cellular aging and oxidative stress (Mishra et al. 2021). Even though the free radical elimination was observed, it seemed lower than that of ascorbic acid, yet it exceeded the level previously reported by Vamanu et al. (2013) (Mishra et al. 2022).

The mushroom has other bioactive substances such as phenols, flavonoids, and alkaloids (Ogidi et al. 2021). Polyphenols donate electrons or atoms of hydrogen to neutralize free radicals (Beslo et al. 2023). Furthermore, fenton reaction is decreased by flavonoids and other components of *P. ostreatus* extract, thus decreasing oxidative stress (Abe et al. 2022). Their fruiting bodies contain numerous diverse bioactive compounds, especially polysaccharides (β-glucans such as "pleuran"), the unusual thiol amino acid ergothioneine, which contribute to brain health (Sreedharan et al. 2025). Moreover, ergothioneine can cross the blood–brain barrier and scavenge reactive oxygen species (ROS), and plays a vital role in protecting against neurodegenerative diseases (Leow et al. 2024). On the other hand, *P. ostreatus* polysaccharides (POP) especially the β-glucans upregulate CAT, SOD, and GPx (Liuzzi et al. 2023). POP inhibited tau phosphorylation and aggregation of the peptide Aβ. The mechanism by which neuroinflammation is decreased is through activating Nrf2/ARE antioxidant-response pathway, promoting glutathione levels, and increasing antioxidant enzymes, thus aging is also delayed (Peng et al. 2023).

Antioxidant activity based on DPPH radical eliminating activity was compared with ascorbic acid, and it was found that with the increase in concentration, scavenging activity also increased. A similar pattern is seen in hydrogen peroxide and nitric oxide eliminating activity (Effiong et al. 2024). In addition, linoleic acid in the ethanol extract of *P. giganteus* induces nerve growth factor synthesis and neurite outgrowth in rat neuroblastoma and pheochromocytoma cells (Phan et al. 2012).

In a recent study, purified polysaccharide (PSP2-1) from *P. sajor-caju* saved rat hippocampal neurons (HT22 cells) from oxidative stress-induced apoptosis from hydrogen peroxide, through the MAPK pathway (Liu et al. 2022). *P. ostreatus* polysaccharides improved cognitive ability in Alzheimer's disease rat models (Zhang et al. 2016b). Meanwhile, in another study, *P. eryngii* extract was evaluated for depression and showed high antidepressive effects, revealing that it produces the derivatives of tryptamine and helps to prevent the toxicity of purified tryptamine (Park et al. 2021). Aminothioneine, extracted from golden oyster mushrooms (*P. cornucopiae* var. *citrinopileatus*), promoted the expression of BDNF by stimulating N-methyl-D-aspartate receptor (NMDAR)-derived Ca2+ signals, which then, in turn, activate cAMP-response element-binding protein (CREB)-dependent transcription in neurons. Thus, cognitive enhancement and effects similar to antidepression can be elicited (Fukuchi et al. 2021). In sum, *Proteus* spp. has anti-inflammatory and antioxidant activity against oxidative stress, antidepressant effects, and improves cognitive function.

5.11 *Grifola frondosa*

Grifola frondosa is a culinary mushroom known widely as "hen of the woods" or "maitake." (Tang et al. 2024). In China, it is known as "hui-shu-hua" or "gray tree flower," and has numerous bioactive compounds, which provide anti-obesity, immunomodulatory, antioxidant, antidiabetic, anti-inflammatory, anti-aging, and anticancer functions (Camilleri et al. 2024). Polysaccharides, especially β-glucans

(D-fraction and X-fraction proteoglucans), are responsible for most of the functions mentioned above. It also contains ergosterol, and derivatives such as ergothioneine, which is a potent antioxidant that decreases the risk of developing Parkinson's disease and mild cognitive impairment by decreasing α-synuclein accumulation (Tripodi et al. 2022).

Neuroinflammation triggers neurodegeneration according to Kempuraj et al. (2016), *G. frondosa* extract *o*-orsellinaldehyde acted against neuroinflammation by decreasing nitric oxide (NO) levels and expression of iNOS in astrocytes and microglia, and computational evidences show that it can cross the blood–brain barrier. In addition, o-orsellinaldehyde inhibits NF-κB activation and MAPK pathways, specifically targeting p38 kinase and c-Jun N-terminal kinase (JNK) phosphorylation. Furthermore, the conformity of microglia toward the M2 macrophage, which is anti-inflammatory while decreasing the pro-inflammatory heme oxygenase-1 (HO-1), is maintained by o-orsellinaldehyde (Tomas-Hernandez et al. 2021). Enhancement in memory and learning in rat models was established by decreasing the accumulation of lipofuscin, which causes cellular damage and dysfunction of mitochondria that leads to oxidative stress. Moreover, *G. frondosa* polysaccharides upregulated the SOD, CAT, and GPx, and decreased the levels of nitric oxide (NO) and MDA (Chen et al. 2017). In a study conducted, polysaccharides from *G. frondosa* improved learning in APP/PS1 mice, which showed alleviation of shrunken neurons and structural integrity in the hippocampus, revealing the neuroprotection function. Furthermore, the clearance of Aβ protein by employing microglia and activating astrocytes is the mechanism underlying the neuroprotective function (Bai et al. 2019).

Receptor for polysaccharides of *G. frondosa* is dendritic cell-associated C-type lectin-1 (Dectin-1), which gets activated by proteo-β-glucan, and the receptor is expressed on microglial cells, macrophages, and dendritic cells. In depression, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) levels are lower, and the polysaccharide activates the Dectin-1/AMPA pathway, and at the synapse, upregulates the AMPA receptors, which in turn brings about the antidepressive effect without any dependence, as seen with other drugs such as ketamine (Bao et al. 2016).

In a study with worm model, *G. frondosa* extract (GE) upregulated skn-1, an ortholog of the NRF2 gene, which is a transcription factor for processes involving antioxidant, as well as antiaging reactions. Besides, it also resulted in overexpression of Nrf in regulating oxidative stress. Thus, it extends the life span and acts as an antiaging agent (Aranaz et al. 2021). The anti-inflammatory property of *G. frondosa* is brought by not worsening the inflammatory response, thus it safely stimulates macrophages without causing cell inflammation (Xu et al. 2023).

5.12 *Hericium erinaceus*

Hericium erinaceus, also known as lion's mane, is edible and has been used for centuries in traditional medicine. It is called "Yamabushitake" in Japan and "Houtou" in China (Sokół et al. 2016). *H. erinaceus* has high- and low-molecular-weight bioactive compounds. High molecular weight compounds include polysaccharides and polypeptides that are involved in reinforcing the immune system. On the other hand, low molecular weight compounds include terpenoids (such as hericenones and erinacines) and polyketides, which have anti-inflammatory, anticancer, and antioxidative qualities (Ratto et al. 2019). Erinacines and hericenones are able to cross the blood–brain barrier (Hu et al. 2019). In addition, polysaccharides extracted from *H. erinaceus* depicted neurogenesis, muscle regeneration, and peripheral nerve formation after trauma and injury (Wong et al. 2011). Moreover, oligosaccharides, which were water soluble and isolated from the lion's mane mushroom, revealed antioxidant properties (Hou et al. 2015). Erinacines cross the blood–brain barrier and promote the synthesis of nerve growth factor (NGF), which is one of the neurotrophins, thus enabling neurite outgrowth (Li et al. 2018). Furthermore, erinacine A decreased microglia and astrocytes activated by plagues and induced the NGF and helped in hippocampal neurogenesis in Alzheimer's disease mouse models (Tsai-Teng et al. 2016). Ergothioneine administered to mice revealed low IL-6 levels along with TGFβ1 in the hippocampus (Roda et al. 2023). Through protein kinase A signaling, hericenone E stimulates the growth of nerves by inducing NGF production and increasing the expression of the NGF gene (Phan et al. 2014). Moreover, erinacine D can stop the transcription of NF-kB triggered by tumor necrosis factor-alpha (TNFα) (Li et al. 2014).

Improved recognition and synaptic activity were observed in mossy fiber-CA3 in mouse hippocampal regions, depicting that *H. erinaceus* can reinforce neuronal pathways and functions even in the absence of pathology (Brandalise et al. 2017). In a clinical trial conducted in Japan, *H. erinaceus* was administered orally for improving mild cognitive impairment, and cognitive scores increased positively with a prolonged administration period (Mori et al. 2009).

Hericenone C is shown to inhibit the expression of inducible nitric oxide (iNOS), which is elevated in oxidative stress, thus decreasing the production of nitric oxide (NO). Furthermore, reduced expression of NF-κB protein and IκBα phosphorylation (p-IκBα) were also confirmed, and hericenone hindered Kelch-like ECH-associated protein 1 (Keap1) but increased Nuclear Factor erythroid 2-related factor 2 (Nrf2) transcription factor and the expression of heme oxygenase-1 (HO-1), which suggests that it activates Nrf2/HO-1 pathway, while inhibiting the synthesis of iNOS, p-IκBα, and IκB (Wang et al. 2019). *H. erinaceus* also reduces peroxidation and enhances scavenging of free radicals (Hsu et al. 2023). In a recent study, erinacine-enriched *H. erinaceus* stimulated NGF and helped maintain structural integrity of arcuate fasciculus (ARC), and parahippocampal cingulum (PHC) with no recorded adverse effects (Li et al. 2020).

Antioxidant activity is exerted by scavenging ROS, and stimulating antioxidant enzymes such as SOD, CAT, and GPx (Lew et al. 2020). It can also act as a calcium

chelator and regulate the level of calcium, thus helping against neurodegenerative diseases, as it is involved in their pathogenesis (Gu et al. 2024). In AD rat models, a decrease in phosphorylation of tau and accumulation of β-amyloid protein were observed, and this is achieved by increasing the Nrf2 transcription factor and other related genes (Cordaro et al. 2021). In addition, through the antioxidant mechanism of Nrf2, neuronal death is prevented, and it helps to protect the brain, as per the study conducted on mouse models (Lee et al. 2024). Furthermore, antidepressant-like effect was studied, and the mechanism was understood through increasing the BDNF and enhancing BDNF/Tropomyosin receptor kinase B (TrkB) signaling (Chong et al. 2021). In sum, *H. erinaceus,* through antioxidant mechanisms and anti-inflammatory properties, promotes healthy brain functioning. Meanwhile, it helps to delay the progression of neurodegenerative diseases.

5.13 Conclusion

Beneficial effects of medicinal mushrooms on human health have been evaluated by many studies, as they are varied and a rich source of bioactive compounds. The mechanism of action of these compounds indicates their extensive therapeutic potential. Polysaccharides such as β-glucans, phenolic compounds, terpenoids, ergothioneine, and lectins are just some of their plentiful bioactive compositions. The health-promoting impact of the medicinal mushrooms is due to their immunomodulatory, antioxidant, antitumor, neuroprotection, cognitive, anti-inflammatory, hepatoprotective, and antiaging effects. The antioxidant attributes of these mushrooms are exerted via mechanisms such as direct scavenging and improving of endogenous antioxidant defenses through the upregulating of antioxidant enzymes like SOD, CAT, and GSH-Px mediated by Nrf2 activation. The results of their effects are crucial in maintaining redox homeostasis and preventing damage to tissues. Mushrooms such as *G. lucidum*, *H. erinaceus*, *C. versicolor*, *Pleurotus* spp., and *G. frondosa* have been shown to exhibit multifaceted protection against neurodegenerative diseases like Alzheimer's and Parkinson's by impacting both pathological and physiological conditions of the body. This impact is implemented by mechanisms like elevating neurotrophic factors like BDNF and NGF, modulating signaling pathways such as PI3K/Akt and MAPK, and also the bioactive compounds' ability to cross the blood–brain barrier, thereby affecting the nervous system.

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6 Medicinal Mushrooms and Mental Disorders: How Mushrooms Affect Anxiety and Depression

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Abstract

Depression and anxiety are the leading prevalent mental health disorders globally, significantly contributing to disability and reduced quality of life. Scientific interest in medicinal mushrooms as alternative or complementary treatments for depression and anxiety is rapidly increasing. These natural compounds are being explored for their potential to address limitations of conventional pharmacological therapies, which are often associated with side effects, delayed onset of action, and treatment resistance. Several medicinal mushroom species,—such as *Hericium erinaceus*, *Cordyceps militaris*, and *Ganoderma lucidum*—have demonstrated neuroprotective, anti-inflammatory, and mood-regulating properties in preclinical studies and early-stage clinical research. These effects are mediated by mechanisms such as modulajtion of serotonin receptors, anti-inflammatory activity, enhancement of neuroplasticity, and gut–brain axis regulation. Despite promising outcomes, major challenges remain. These include legal and ethical barriers, dosing inconsistencies in natural products, lack of large-scale randomized clinical trials, and limited understanding of long-term safety. It concludes by calling for more rigorous clinical research and standardized methodologies to support the integration of mushroom-based therapies into mainstream mental health care.

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Keywords

Medicinal mushrooms · Psilocybin · Depression · Anxiety · Regulatory barriers

6.1 Introduction to Medicinal Mushrooms and Mental Health

According to the World Health Organization (WHO), depression is a prevalent mental disorder impacting over 322 million individuals globally (Moreno-Agostino et al. 2021). Depression ranks among the primary contributors to physical and mental disability globally. The genesis of depression involves a complex interaction of biological, psychological, and social elements (Dhar and Barton 2016; Galts et al. 2019).

Anxiety disorders are psychosocial problems linked to generalized or context-specific reactions to perceived dangers (Tian-Ci Quek et al. 2019). Approximately 4.05% of the global population experiences an anxiety illness, totaling 301 million individuals. Anxiety disorders rank among the most prevalent mental health conditions. They typically manifest early in infancy and, akin to other mental diseases, exhibit a chronic trajectory and significant functional repercussions (Javaid et al. 2023). The population impacted has risen by around 55% from 1990 to 2019. Metrics for anxiety disorders indicate a persistent rise in prevalence, incidence, and disability-adjusted life years (DALYs) (Xiong et al. 2022).

Clinical psychopharmacology is a scientific discipline that delineates the application of pharmacological substances for the treatment of particular mental disorders (Ban 2001). The discipline originated in the 1940s and 1950s. Iproniazid, originally released in 1952 as a treatment for tuberculosis, became the first drug used to treat depression (Bloch et al. 1953).

Medicinal and edible mushrooms, along with their mycelia from in vitro cultures, have gained increasing scientific attention due to their potential health benefits. Classified as functional foods, they produce various metabolites that support physical and mental well-being, making them valuable as dietary supplements. Research highlights their antioxidant, anticancer, anti-inflammatory, and immune-boosting effects. There is a growing number of research supporting their antidepressant and anti-anxiety efficacy (Muszynska et al. 2018).

This chapter aims to investigate the role of medicinal mushroom compounds in mental health management, with a particular focus on depression and anxiety. This includes an overview of the effective mushroom species, their mechanisms of action, and the limitations and challenges associated with their use.

6.2 Exploring Therapeutic Potential of Medicinal Mushrooms in Depression and Anxiety

Depression and anxiety are the most prevalent mental health disorders globally, impacting about 280 million and 301 million people. Additionally, global prevalence rates increased by over 25% in the course of the 2019 coronavirus pandemic (Santomauro et al. 2021). Depression can appear in several forms, with the most types common being major depressive disorder (MDD) and persistent depressive disorder. MDD involves severe depressive symptoms lasting at least 2 weeks and affecting daily functioning, while persistent depressive disorder features less intense symptoms that continue for 2 years or longer. Other forms include perinatal or postpartum depression, seasonal affective disorder, psychotic depression, and bipolar disorder which is characterized by depressive episodes alternating with manic phases (Lam 2018; Lew et al. 2020). Depression ranks among the primary causes of disability affecting both mental and physical health across the globe. Its development involves a complex interaction between psychological, social, and biological elements. Individuals who have encountered negative life experiences, such as the loss of a loved one or extended unemployment, face a heightened chance of developing depression (Dhar and Barton 2016; Galts et al. 2019). Anxiety is a widespread psychological symptom among patients facing terminal illnesses. Factors such as treatment process, disease progression, persistent pain, dying, and the unpredictability of death can significantly worsen their situation (Passik et al. 2001). The rising incidence of anxiety globally poses a substantial risk to the well-being and quality of life of individuals (Javaid et al. 2023). Anxiety also hinders recovery from medical procedures and is linked to shorter survival times in terminally ill patients (Groenvold et al. 2007). The therapeutic approach in depression is rooted in the monoamine hypothesis, proposed in the 1960s, which posits that the disorder stems from reduced levels of brain monoamines including serotonin, norepinephrine, and dopamine (Perez-Caballero et al. 2019). Antidepressants and benzodiazepines are frequently used to manage depression and anxiety in patients facing critical illnesses (Rayner et al. 2011). Despite their common use, there are currently no FDA-approved pharmacotherapies specifically for the psychological distress associated with life-threatening illnesses. Moreover, a key challenge with antidepressants is their delayed onset of clinical improvement. This, combined with high relapse rates and the occurrence of significant side effects, often makes it difficult for patients to adhere to their treatment regimens (Reynolds et al. 2009). Although existing treatments help many, some patients remain symptomatic, cannot tolerate the therapy, experience negative side effects, or encounter withdrawal (Davis et al. 2021; Gartlehner et al. 2016). Recently, researchers have reignited interest in psychedelic substances as an emerging treatment option. One of these compound is psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine), a naturally occurring plant alkaloid that acts as a 5-HT2A receptor agonist. Early studies on psilocybin have mainly focused on its use in treating anxiety and depression (Carhart-Harris et al. 2018; Griffiths et al. 2016; Ross et al. 2016). Medicinal mushrooms are classified as functional foods since they synthesize and accumulate various metabolites that enhance

their health-promoting properties. A wealth of evidence indicates that introducing medicinal or edible mushrooms in the daily diet—either in dishes or as supplements—may reduce the risk of developing depression. These compounds have anti-neuroinflammatory and antioxidant effects, which involved in regulating neurotrophin levels, promoting the neurogenesis, and affecting the gut–brain axis (Lazur et al. 2023). Lew et al. (2020) explore the increasing interest in medicinal mushrooms as alternative treatments for depression. These natural compounds are generally well-tolerated and show promise as safe supplements or therapeutic agents. Their potential in managing depression and anxiety is attributed to their neuroprotective, anti-inflammatory, and cholinesterase-inhibiting properties. However, further research is needed in order to confirm their efficacy, improve delivery methods, and facilitate integration into modern drug development frameworks. A double-blind, placebo-controlled trial found that giving cancer patients a single moderate dose of psilocybin, along with psychotherapy, led to rapid and long-lasting reductions in anxiety and depression—effects that lasted for up to 8 months. Participants also showed improved quality of life, spiritual well-being, and attitudes toward death (Ross 2016). In meta-analysis of four studies ($N = 117$), Goldberg et al. (2020) found that psilocybin combined with behavioral support produced large, marked improvements in anxiety and depression symptoms, with no serious side effects observed. Psilocybin significantly eased depression and anxiety symptoms in patients with life-threatening illnesses, showing strong improvements on various psychological scales (Vargas et al. 2020). Findings of a large prospective survey showed lasting improvements in anxiety, depression, and well-being, with most users reporting positive outcomes of naturalistic psilocybin. Additionally, potential mental health benefits of psilocybin outside clinical settings have been suggested (Nayak et al. 2023). The potential of medicinal mushrooms, particularly *Ganoderma lucidum* and *Hericium erinaceus*, in improving mood, cognitive function, and overall well-being has been highlighted. Early clinical evidence suggests benefits for depression, anxiety, and cognitive decline, with low risk and good safety profiles (Lee 2023).

Preclinical studies highlight psilocybin's therapeutic potential across various neuropsychiatric conditions, particularly depression. Evidence suggests that psilocybin promotes neuroplasticity and alters functional brain connectivity, potentially restoring dysfunctional neural networks (Gattuso et al. 2024). The Cochrane review analyzed randomized trials of psychedelic-assisted therapy for anxiety, depression, and existential distress in patients with life-threatening illnesses. Findings suggest potential effectiveness of psilocybin and lysergic acid diethylamide (LSD) in medical settings, though the evidence is of low to very low certainty (Schipper et al. 2024). In a phase 2 trial, Weiss et al. (2024) found that the antidepressant effects of psilocybin therapy are strongly linked to the unique psychological experiences—particularly mystical experiences, ego dissolution, and emotional breakthroughs—which distinguish it from traditional selective serotonin reuptake inhibitors (SSRI) treatment. Psilocybin shows promise as a novel treatment for post-traumatic stress disorder (PTSD), with antidepressant, anxiolytic, and fear-extinction effects demonstrated in preclinical and clinical studies. While current treatments are often

ineffective, more research is needed to address limitations such as dose variability, sex differences, and hallucinogenic side effects (Miller and Zoladz 2025). Evidence suggests that psilocybin promotes neuroplasticity and alters brain connectivity, supporting its promise as a safe and effective option for treating psychiatric disorders, though limitations such as small sample sizes, bias, and limited generalizability highlight the need for further clinical and mechanistic research (Goldberg et al. 2020; Lee 2023; Vargas et al. 2020).

6.3 Mushrooms in the Context of Alternative and Integrative Therapies

Medicinal mushrooms are placed within the broader landscape of treatments for anxiety and depression, and here we explore how they can complement or replace existing treatments. Here, we see that mushrooms are one piece of a larger puzzle in mental health care.

6.3.1 Therapeutic Effects of Culinary and Medicinal Mushrooms in Managing Depression and Anxiety

Mushroom compounds have been commonly used by physicians, herbalists, naturopaths, chiropractors, acupuncturists, and practitioners of traditional Chinese medicine. The therapeutic benefits of medicinal mushrooms are strongly connected to their activity spectrum, as evidenced by in vitro and in vivo investigations, which consider substrate sources, extraction techniques, dosage, and the length and frequency of administration. This analysis examines nine medicinal mushrooms and compiles the existing research that highlights their possible roles in the prevention and management of anxiety and depression (Table 6.1). Animal models are commonly used to study antidepressant effects and uncover the brain mechanisms underlying depression, aiding the development of new therapies (Capra et al. 2010). These models typically involve subjecting animals to stress before evaluating their behavioral responses. The primary methods used to assess the effectiveness of antidepressants are the tail suspension test (TST) and the forced swim test (FST) (Can et al. 2012; Yankelevitch-Yahav et al. 2015). Both assessments rely on monitoring the animal's escape behavior, exemplified by adopting an immobile stance when subjected to a brief, inescapable, and unpleasant scenario. This immobility, referred to in animals as behavioral despair, is thought to induce a state akin to human depression, and a decrease in overall immobility duration signifies an antidepressant effect (Porsolt et al. 2001).

New preclinical research suggests that extracts from medicinal mushrooms can have effects similar to those of anxiolytic drugs in animals. For example, experiments using extracts from species such as *H. erinaceus* and *G. lucidum* have shown a reduction in anxiety-like behaviors. Researchers often use behavioral tests like the Elevated Plus Maze (EPM), where time in open arms reflects lower anxiety, and the

Table 6.1 A summary of types of mushrooms and their effects on depression and anxiety

Mushroom	Effect on depression	Effect on anxiety
Agaricus bisporus	Polysaccharide extracts (e.g., glucogalactan) stimulate the synthesis of key neurotransmitters (norepinephrine, dopamine, serotonin) in animal models, suggesting neuroprotective and antidepressant potential	Primarily studied for its antidepressant properties; however, its antioxidant, anti-inflammatory, and neurotransmitter-modulating actions indicate potential anxiolytic benefits
A. brasiliensis	Limited direct evidence on depression; its neuroprotective and antioxidant activities may indirectly support mood stabilization	Demonstrates robust anxiolytic effects in animal models. Its aqueous extract significantly reduces anxiety-like behaviors by modulating brain monoamines, reducing oxidative stress, and lowering plasma corticosterone levels
Cordyceps sinensis	Exhibits clear antidepressant-like effects in rodent models via enhanced noradrenergic and dopaminergic transmission, reducing immobility in behavioral tests	Possesses strong anti-stress properties that mitigate physiological stress markers, which may indirectly contribute to reducing anxiety symptoms
C. militaris	The active compound cordycepin produces potent, dose-dependent antidepressant effects in chronic stress models by normalizing neurotransmitter levels, reducing inflammatory cytokines, and enhancing BDNF expression through A-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor signaling	In combination formulations, cordycepin-rich extracts reduce anxiety-like behaviors (e.g., increased open-arm time in the Elevated Plus Maze), likely due to reduced neuroinflammation and normalized neurotransmitter profiles
Ganoderma lucidum	Aqueous extracts and triterpenoids show antidepressant-like effects in rodent models by reducing immobility and modulating serotonergic activity	Findings are mixed; initial studies showed minimal anxiolytic action, but later evidence suggests that its anti-inflammatory properties may help reduce anxiety-like behaviors
Grifola frondosa	Proteo-β-glucan extracts produce significant antidepressant effects in mice by reducing immobility through enhanced dectin-1/A-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor signaling in the frontal cortex	Anxiolytic effects are uncertain; although cognitive benefits are observed, standard anxiety tests did not reveal statistically significant changes
Hericium erinaceus	Ethanolic and standardized extracts (including those fortified with erinacine A) reduce immobility in behavioral tests, enhance hippocampal neurogenesis, restore monoamine balance, and upregulate BDNF, contributing to strong antidepressant-like effects	Reduces anxiety-like behaviors (e.g., less peripheral zone activity in the open field test) and improves sleep quality, as supported by both animal studies and clinical pilot trials

(continued)

Table 6.1 (continued)

Mushroom	Effect on depression	Effect on anxiety
Lentinus edodes	Lentinan, a polysaccharide extracted from shiitake mushrooms, shows strong antidepressant effects in rodent studies by boosting Dectin-1 and A-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activity in the prefrontal cortex	No specific evidence regarding anxiolytic effects is provided, leaving its impact on anxiety unclear
Pleurotus cornucopiae var. citrinopileatus	Rich in ergothioneine, this mushroom displays notable antidepressant effects by reducing immobility and increasing markers of neurogenesis in depression models	Golden oyster mushrooms contain bioactive compounds that support neuroprotection, cognitive health, and stress reduction, potentially aiding anxiety treatment research

Open Field Test (OFT), where center exploration suggests reduced anxiety. In addition, the Light-Dark Box Test is also used, where treated animals spending more time in the light area indicates reduced anxiety-like behavior. Together, these experiments provide a robust framework for judging how well mushroom extracts can help animals with anxiety. However, while the results of these animal studies are intriguing, further studies are needed to validate efficacy, uncover underlying mechanisms, and examine the clinical implications of these discoveries for human anxiety disorders (Venturella et al. 2021; Wang et al. 2024).

6.3.1.1 *Agaricus bisporus*

A. bisporus (Fig. 6.1) is a widely cultivated mushroom species and is known by various names such as button mushroom, white mushroom, portobello, Swiss brown, and table mushroom (Wong et al. 2017). It is widely grown across the United States, Europe, and parts of Australia (Roupas et al. 2010). Glucogalactan (GA), a polysaccharide from *A. bisporus*, was tested in a rat model of trimethyltin-induced neuropathy.

GA was administered at a dose of 300 mg/kg. After 28 days, the treatment enhanced neurotransmitter synthesis in the brain, indicating its potential neuroprotective properties (Hassan et al. 2015). Brain analysis showed elevated levels of norepinephrine (NE), dopamine (DA), and serotonin (5-HT)—neurotransmitters linked to depression. The polysaccharide also caused no neuropathological damage, with normal structures preserved in key brain regions.

Most of the reputable preclinical research on *A. bisporus* (J.E. Lange) Imbach has looked at its potential as an antidepressant. New evidence suggests that its mood-boosting effects may also help with anxiety. In animal studies, extracts of *A. bisporus* have been linked to better behaviors that are connected to depression. Although dedicated anxiety assays (e.g., EPM or OFT) have been less frequently

Fig. 6.1 *Agaricus xanthodermus* (Agaricaceae), Germany. (Photo Rolf Faber) (Gafforov et al. 2023)

employed, the underlying pharmacological actions—such as antioxidant effects, anti-inflammatory properties, and modulation of neurotransmitter systems—provide a rationale for its potential anxiolytic benefits. In other words, even though most of the research thus far has focused on its antidepressant benefits, these results show that *A. bisporus* may also help with anxiety symptoms in animal models. More specialized studies are needed, nevertheless, to explicitly examine this effect using anxiety-specific behavioral tests (Bose et al. 2019; Sinha et al. 2025).

6.3.1.2 *Agaricus brasiliensis*

A. brasiliensis (synonyms: *A. blazei*, *A. subrufescens*, and *A. rufotegulis*) (Fig. 6.2) is a mushroom species native to Brazil. It is popularly known as the royal sun mushroom or almond mushroom, and by regional names such as himematsutake in Japan and Ji Song Rong in China. This mushroom is widely cultivated in countries like Japan, the United States, Denmark, and the Netherlands (Lisiecka et al. 2013).

The aqueous extract of *A. brasiliensis* (AbSE) reduced ischemia-induced anxiety in rats, as assessed by EPM and social interaction tests following middle cerebral artery occlusion (Zhang et al. 2015). EPM is a common behavioral test used to evaluate emotional reactivity anxiety and behaviors related to anxiety in mice, first developed by Walf and Frye (2007). The Elevated Plus Maze (EPM) tests anxiety by measuring rats' preference for enclosed versus open arms. Daily treatment with 8 and 10 mg/kg AbSE for 30 days increased time and entries into open arms and improved social interaction in rats. The treatment lowered elevated cortical monoamines and plasma corticosterone, reduced lipid peroxidation, and enhanced

Fig. 6.2 *Agaricus brasiliensis* fruiting bodies: Different stages of maturation (de Miranda 2022)

antioxidant enzyme activity. The findings point that AbSE might help relieve anxiety caused by cerebral ischemia/reperfusion by lowering oxidative stress. Studies on animals have shown that *A. brasiliensis* may have strong effects in reducing anxiety. In one study, giving rats with brain ischemia an extract of *A. brasiliensis* (AbSE) by mouth caused their anxiety-like behaviors to drop significantly. Using traditional behavioral tests, including social interaction tests and the elevated plus maze test, it was shown that treated mice explored regions that worried animals usually avoid. In addition to reducing anxiety, the drug also caused good changes in the brain's chemistry, such as higher levels of brain monoamines (noradrenaline, dopamine, and serotonin), lower levels of oxidative stress, and lower levels of plasma corticosterone. The extract did not cause extrapyramidal side effects, as shown by the catalepsy test. This suggests that it may be safe to study more. Together, these data indicate that the therapeutic potential of *A. brasiliensis* in relieving anxiety symptoms in animal models may be mediated by a combination of neuroprotective and antioxidative mechanisms (de Miranda 2022; Zhang et al. 2015).

6.3.1.3 *Cordyceps militaris*

C. militaris (Fig. 6.3), sometimes referred to as Northern Worm Grass Mushroom or Bei Chong Cao in Chinese, is a parasite of the larvae or pupae of Lepidoptera moths. The fungus has been used as a tonic in China for centuries. The primary active component is cordycepin, a nucleoside analog of 3′-deoxyadenosine extracted from the culture medium of *C. militaris* (Tuli et al. 2017). Cordycepin consists of an adenine

Fig. 6.3 Scarlet Caterpillarclub (*Cordyceps militaris*)

base linked to a deoxyribose sugar and is known to affect various cellular signaling pathways. These include controlling programmed cell death, cell growth, cancer spread, new blood vessel formation, and inflammation (Tuli et al. 2017). Cordycepin showed potential antidepressant effects in ICR mice exposed to prolonged unpredictable mild stress (Tianzhu et al. 2014). Giving 20 and 40 mg/kg of cordycepin orally during the last 3 weeks of a 6-week stress period significantly increased sucrose intake, decreased immobility time in both TST and FST, restored normal levels of TNF-α, IL-6, serotonin, and norepinephrine in the hippocampus, and boosted the expression of brain-derived neurotrophic factor (BDNF) in that region.

Similarly, intraperitoneal doses of 5 mg/kg and 12.5 mg/kg of cordycepin elicited swift and significant antidepressant effects in the CD-1 mouse model during the TST and FST (Li et al. 2016). The effects were markedly swifter and more powerful than those of imipramine. Cordycepin increased phosphorylation of GluR1-S845 and GluR1 proteins in both the prefrontal cortex and hippocampus. These effects were blocked when the specific AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor antagonist GYKI 52466 was given beforehand. This suggests that AMPA receptors play a key role in mediating the rapid excitatory synaptic responses in the central nervous system induced by cordycepin. Preclinical

Fig. 6.4 Fungus *Cordyceps sinensis*

investigations have shown that *C. militaris* may be able to help with anxiety. One important study used an unexpected chronic mild stress (UCMS) model in rats to test a combination formula that included Poria cocos and a waste medium extract of *C. militaris* (which is very high in cordycepin) to see how it affected mood. Rats given the extract spent significantly more time in the EPM's open arms, indicating reduced anxiety. These changes in behavior were also linked to lower levels of pro-inflammatory cytokines and changes in neurotransmitter systems. This suggests that the anxiolytic effects could be due to less neuroinflammation and normalizing levels of brain monoamines. These findings indicate *C. militaris* may help treat anxiety, but more research is needed to determine optimal dosing, safety, and real-world effectiveness (Huang et al. 2020).

6.3.1.4 *Cordyceps sinensis*

C. sinensis, also called *Ophiocordyceps sinensis* (see Fig. 6.4), is an endophytic fungus that grows inside and feeds on the dead larvae of Hepilus moths (Martel et al. 2017). Koh et al. (2003) found that a hot water extract derived from the mycelium of *C. sinensis* showed stress-relieving effects in rats exposed to immobilization stress (Koh et al. 2003). Typical stress responses include weight changes, reduced food intake and activity, organ size shifts (thymus and spleen shrink, adrenal glands enlarge), lymphocyte loss, altered white blood cell counts, and impaired reproduction.

Pretreatment with 150 mg/kg of the hot water extract for 8 days reduced stress-induced weight changes in the adrenal gland, thymus, and thyroid after 48 h of immobilization. A supercritical extract of *C. sinensis* given orally (2.5–10 ml/kg) for 5 days reduced immobility in the Tail Suspension Test in young male mice, with stronger effects at higher doses. To explore monoamine involvement, mice were

given the α_1-adrenoceptor blocker prazosin and the dopamine D_2 receptor blocker sulpiride 45 min before testing. These blockers prevented the extract's antidepressant effect, suggesting a role for noradrenergic and dopaminergic pathways (Koji et al. 2007). *C. sinensis* showed antidepressant effects in streptozotocin-induced diabetic rats. Daily treatment with vanadium-enriched extract for 4 weeks reduced immobility in the forced swim test, normalized blood sugar, and increased insulin, suggesting potential for treating depression in diabetes (Guo et al. 2011). Vanadium (V) is a trace element characterized by its silvery-white color and lack of odor, with an atomic mass of 50.941 (Schroeder 1970). This stable transition metal is insoluble in water and occurs naturally in approximately 65 mineral compounds. Vanadium, naturally present in human tissues, supports insulin signaling and acts as an antidiabetic agent due to its insulin-mimicking effects. Studies report its levels in placenta, kidney, liver, and muscle ranging from 0.5 to 7.5 ng/g (Gil et al. 1988; Han et al. 2008).

6.3.1.5 *Ganoderma lucidum*

G. lucidum (Fig. 6.5), commonly known as Reishi or Lingzhi, is a revered mushroom in traditional Chinese medicine and has been consumed by Asian cultures for thousands of years as a dietary supplement, often prepared as tea, soup, or other forms. It was recorded in the ancient Qin Dynasty text *Shen Nong Ben Cao Jing* (221–206 BC), one of the earliest works on herbal medicine (Yang 1998). Oral administration of 1 g/kg lyophilized mycelial extract produced antidepressant-like

Fig. 6.5 *Ganoderma lucidum*

effects in rats, reducing anxiety in the forced swim test, freezing in fear conditioning, and head twitches induced by 5-HT2A activation (Matsuzaki et al. 2013; Socala et al. 2015).

The head-nod response, involving quick movements of the head and neck, is commonly used in mouse research to assess how drugs affect serotonin activity in the brain. Socala et al. (2015) confirmed the extract's antidepressant-like effect by showing reduced immobility time in rats during FST. However, the extract did not show any anxiety-reducing effects (Socala et al. 2015). In a study using mice experiencing psychomotor seizures triggered by 6 Hz stimulation, the extract demonstrated a minimal anticonvulsant effect. However, it did not provide any seizure protection in tests involving acute maximal electroconvulsive seizures or after intravenous pentylenetetrazole administration. Recent research in animals that haven't yet been tested on people suggests that *G. lucidum* may help with anxiety. Researchers looked at how *G. lucidum* triterpenoids affected mice that had been separated from their mothers. This is a paradigm that causes behaviors similar to anxiety and despair. The treatment significantly reduced anxiety-related behavior by lowering the inflammatory response in both the brain and peripheral tissues. This suggests that the drug's anti-inflammatory characteristics may be what make it work. In another study, polysaccharides from *Ganoderma* species showed significant anxiolytic-like activity in mice as measured by EPM. The treated mice spent prolonged time in the open arms, which is a sign of less anxiety, without showing any sedative effects. These results show that *G. lucidum* ingredients could be useful for lowering anxiety by protecting the brain and reducing inflammation. However, more studies, especially in clinical settings, are needed to confirm these effects (Mi et al. 2022; Veronica et al. 2021).

6.3.1.6 *Grifola frondosa*

G. frondosa (Fig. 6.6) is a mushroom recognized by several names around the world: gray tree flower in China, Mitake in Japan, forest chicken in North America, and ram's head in Germany, and it naturally grows throughout Japan, China, Europe, and the United States.

A proteo-β-glucan fraction isolated from the D protein extract of *G. frondosa*—prepared via 95% ethanol precipitation and supplied by Mushroom Wisdom Inc. (East Rutherford, NJ, USA)—demonstrated antidepressant-like effects in CD-1 mice (Bao et al. 2016).

Intraperitoneal proteo-β-glucan produced dose-dependent antidepressant effects in TST and FST after both acute and 5-day treatments. It increased Dectin-1 and GluA1-S845 receptor activity in the prefrontal cortex, effects blocked by Dectin-1 or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist (GYKI 52466), suggesting a novel antidepressant mechanism via Dectin-1 and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) signaling (Bao et al. 2016).

In CD-1 mice, supplementation with *G. frondosa* powder mixed into standard chow led to a significant reduction in immobility time during both TST and FST (Bao et al. 2017a). The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

Fig. 6.6 *Grifola frondosa*

(AMPA) antagonist GYKI 52466 blocked the antidepressant effects, suggesting *G. frondosa* may enhance α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor signaling as a key mechanism. A study on mice found that 14 days of oral *G. frondosa* extract (100 or 200 mg/kg) improved spatial learning and memory, as shown by better performance. However, the Morris Water Maze (MWM) and Light-Dark Transition tests did not show any statistically significant changes in anxiety-related behaviors. These results imply that *G. frondosa* may improve some elements of cognitive function, but it is still unclear if it may help with anxiety in this animal model. This shows that more study is needed with different anxiety-focused paradigms or modified procedures (Fadilah et al. 2023).

6.3.1.7 *Hericium erinaceus*

H. erinaceus (Fig. 6.7) is a distinctive fungus identified by its long, pale spines and is commonly known by several names, including lion's mane, monkey head mushroom, hedgehog mushroom, and Yamabushitake. It naturally grows in temperate forests across North America, Europe, and Asia (Mizuno 1999; Wong et al. 2009). It is also widely used in traditional Chinese and Japanese cuisine. Oral doses of 20 and 60 mg/kg *H. erinaceus* extract for 28 days reduced immobility in TST and FST, suggesting antidepressant effects. The higher dose also reduced time spent at the edge in the open field test (OFT).

Increased Proliferating Cell Nuclear Antigen (PCNA) and Ki67 levels suggest enhanced hippocampal cell proliferation, while higher doses also boost neurogenesis, shown by more 5-bromo-2′-deoxyuridine (BrdU) and BrdU/NeuN-positive cells in the dentate gyrus (Ryu et al. 2018).

Fig. 6.7 The fungus *Hericium erinaceus* (referred to as lion's mane mushroom)

Elevated pro-inflammatory cytokines are linked to stress and depression. Amycenone, a standardized *H. erinaceus* extract (0.5% hirsinones, 6% amyloban), was tested for anti-inflammatory and antidepressant effects in Lipopolysaccharide (LPS)-treated C57BL/6 N mice (Yao et al. 2015). A single oral dose of Amycenone (50–200 mg/kg) reduced LPS-induced inflammation and immobility in TST and FST, while erinacine A-enriched extract (200–400 mg/kg) showed similar antidepressant effects in stressed mice. These benefits were linked to reduced inflammation, restored monoamine levels, activation of the PI3K/Akt/GSK-3β pathway, and increased BDNF expression. The treatment enhanced hippocampal NE, DA, and 5-HT levels by reducing stress-induced interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) and restoring brain-derived neurotrophic factor (BDNF), tropomyosin receptor kinase B (TrkB), phosphoinositide 3-kinase (PI3K), phosphorylated Akt (Akt-p), and phosphorylated glycogen synthase kinase 3 beta (GSK-3β-p) (Chiu et al. 2018).

Erinacine A (C25H36O6) is a diterpenoid compound with a molecular weight of 432.5. This small compound from *H. erinaceus* mycelium aids neuroprotection by boosting nerve growth factor (NGF) through its diterpenoid derivatives (Phan et al. 2014). In a study of 30 women (avg. age 41.3), daily intake of 0.5 g *H. erinaceus* wheat germ cookies for 4 weeks reduced depression, anxiety, hopelessness, and palpitations (Nagano et al. 2010). An 86-year-old man with recurrent depression showed improved neurocognitive function after treatment with Amyloban® 3399, a standardized *H. erinaceus* extract (Inanaga 2014).

A 4-week study by Okamura et al. (2015) found that Amyloban® 3399 increased salivary 3-methoxy-4-hydroxyphenylglycol (MHPG) levels in female students with sleep issues, a marker linked to anxiety disorders. Increased MHPG levels were linked to improved anxiety symptoms (Okamura et al. 2015). Vigna et al. (2019) studied 77 overweight adults (avg. age 53.2) who took a daily *Hericium*-based supplement for 8 weeks. The treatment improved mood, reduced depression and anxiety, and enhanced sleep, linked to changes in pro-BDNF levels (Vigna et al. 2019).

6.3.1.8 *Lentinus edodes*

L. edodes (Fig. 6.8), commonly known as shiitake in Japan, is one of the most widely cultivated edible mushrooms globally (Wasser 2010). Shiitake ranks second in global mushroom production at around 2 million tons annually. In the 1940s, Japanese growers began outdoor cultivation using inoculated hardwood logs. Lentinan, a -1,3-D-glucan backbone with β-1,6-D-glucopyranoside branches, was first extracted from *L. edodes* fruiting bodies in 1969 (Chihara et al. 1969). Lentinan showed dose-dependent antidepressant effects in mice, linked to increased Dectin-1 and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activity in the prefrontal cortex. These effects were blocked by inhibitors, suggesting lentinan acts via Dectin-1/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) signaling, supporting its potential for depression treatment (Bao et al. 2017b).

6.3.1.9 *Pleurotus cornucopiae* var. citrinopileatus

The golden oyster mushroom (*Pleurotus cornucopiae* var. citrinopileatus) (Fig. 6.9), native to northern China, Japan, and eastern Russia, is widely known by the same common name—the golden oyster mushroom (Lee et al. 2007). Oyster mushrooms are abundant in ergothioneine, a hydrophilic antioxidant amino acid generated from fungi. Ergothioneine (C9H15N3O2S) is classified as an organic chemical within the category of histidine and its derivatives. Ergothioneine is a colorless, odorless compound with high water solubility and concentrations of 1–2 mM in tissues. Due to

Fig. 6.8 *Lentinus edodes* (shiitake)

Fig. 6.9 Yellow oyster mushrooms

limited natural availability, research focuses on enhancing its fungal production (Nguyen et al. 2013).

In a mouse study, synthetic ergothioneine and aminothionine® (a golden oyster mushroom extract) reduced depression-like behavior and boosted neurogenesis by increasing ergothioneine levels in the brain and blood (Nakamichi et al. 2016).

It has been studied for its potential neuroprotective and anti-inflammatory effects, which may contribute to reducing stress and anxiety. The bioactive compounds found in oyster mushrooms, such as beta-glucans and ergothioneine, have been linked to cognitive benefits and neurogenesis. However, specific studies on the direct impact of *P. cornucopiae* var. citrinopileatus on anxiety treatment appear to be limited (Wan Mahari et al. 2020).

6.4 Biological Mechanism of Mushroom Action

Psilocybin is a naturally occurring tryptamine alkaloid prodrug present in mushrooms belonging to the genus *Psilocybe*. Psilocybin shares similar properties with lysergic acid diethylamide (LSD) and mescaline, differing only in its chemical structure (Baumeister et al. 2014). After ingestion, psilocybin is metabolized into Psilocin (Dodd et al. 2023; Ling et al. 2022). After oral intake of psilocybin, psilocin becomes detectable in the plasma within 20 to 30 min and typically reaches its peak concentration between 2 and 3 h (Brown et al. 2017; Kolaczynska et al. 2021).

Psychedelics like psilocybin are substances that induce unusual states of consciousness, characterized by changes in perception, thinking, and mood. These compounds have demonstrated potential therapeutic effects for neuropsychiatric disorders including depression, obsessive-compulsive disorder, and addiction (Nichols 2016; Vollenweider and Preller 2020). Among psychedelics, psilocybin has recently been found to quickly reduce depression symptoms, with effects lasting for months (Carhart-Harris et al. 2016; Davis et al. 2021; Griffiths et al. 2016; Ross et al. 2016). Since 1970, psilocybin has been designated as a controlled substance in the United States, which has limited thorough research into its pharmacological properties (Johnson et al. 2018). The exact biological mechanism of action of psilocybin on psychiatric disorders has remained unclear. However, various mechanisms have been studied and mentioned.

6.4.1 Activation of Serotonin Receptors

Psilocin acts as a full or partial activator of various serotonin receptors, including the 5-HT2A subtype, and also shows moderate stimulating effects on 5-HT1A and 5-HT2C receptors (Baumeister et al. 2014; Kargbo 2020; Passie et al. 2002).

Serotonin 5-HT2A receptors are located throughout various brain regions, including the prefrontal cortex, striatum, ventral tegmental area, and thalamus. Activation of these receptors by psilocybin is linked to psychotic-like effects (Bortolozzi et al. 2010; Thomas et al. 2017).

These receptors are highly expressed in the visual cortex, possibly explaining the visual hallucinations linked to psilocybin use (Watford and Masood 2024).

Compared to ketamine, psilocybin induces more pronounced visual hallucinations but does not produce some of the adverse effects seen with other psychedelics, such as a sense of losing physical control, heightened anxiety, or emotional detachment (Tylš et al. 2014; Vollenweider and Geyer 2001). Some studies have suggested that the re-expression of 5-HT2A receptors in the prefrontal cortex restores anxiety symptoms and, in patients with MDD, correlates positively to the severity and duration of depression (Kometer et al. 2013; Weisstaub et al. 2006). As previously mentioned, psilocybin constantly activates the 5-HT2A receptors through downregulation and desensitization of these receptors due to their overexpression. Psilocybin reduces depressive and anxious symptoms (Van Oekelen et al. 2003).

Moreover, Sakashita et al. (2015) discovered that Psilocin has been found to alter serotonin and dopamine levels in specific regions of the rat brain. Psilocybin increases serotonin in the medial prefrontal cortex via 5-HT2A receptors and boosts dopamine in the nucleus accumbens through 5-HT1A/2A activation. In humans, it also raises dopamine in the caudate and putamen, contributing to euphoria and depersonalization (Vollenweider et al. 1999).

6.4.2 Alternations in the Activity of Various Brain Parts

The thalamus, part of the cortico–striato–thalamo–cortical (CSTC) circuit, filters internal and external stimuli to the cortex, helping regulate consciousness and attention (Alkire et al. 2008; Ferrarelli et al. 2010; Geyer and Vollenweider 2008). Psilocybin activates 5-HT2A receptors in the thalamus, disrupting thalamocortical signaling and overwhelming the cortex, leading to heightened sensory perception, cognitive changes, and ego dissolution—hallmarks of psychedelic, "mystical-like" experiences (Carhart-Harris et al. 2012; Geyer and Vollenweider 2008; Kargbo 2020; Nichols 2004; Passie et al. 2002; Vollenweider and Geyer 2001).

FDG-PET scans of healthy individuals after psilocybin intake showed increased activity in the prefrontal cortex, which correlates with psychotic-like symptoms, especially experiences of ego disintegration. Psilocybin caused an increase in glucose metabolism primarily in the right frontotemporal cortex, with notable effects observed in the right anterior cingulate cortex (Gouzoulis-Mayfrank et al. 1999), which can be explained by the sensory overload activation of the frontal cortex ("hyperfrontality") resulting from thalamic gating disruption (Vollenweider et al. 1997).

6.4.3 Alternations in Brain Connectivity

Psilocybin significantly alters brain activity and disrupts functional connectivity between key brain regions (Grimm et al. 2018; Lord et al. 2019; Müller et al. 2018; Tagliazucchi et al. 2014). Moreover, it has been associated with changes in neuroplasticity (Ly et al. 2018). Resting-state fMRI revealed that psilocybin induced connectivity impairment between distinct brain regions (Calvey and Howells 2018). These brain connectivity changes include the decay of associative networks and the integration of sensory function networks (Nichols 2020). Eventually, psilocybin administration disrupts standard brain connectivity and establishes strong, long-range functional connections that are typically absent (Petri et al. 2014). For instance, it decreased connectivity between the medial prefrontal cortex and the posterior cingulate cortex (Carhart-Harris et al. 2012).

Conversely, there is heightened integration among cortical areas, likely driven by activation of 5-HT2A receptors. This strengthened connectivity can lead to synesthesia—a condition where the activation of one sensory pathway triggers sensations in a different modality. Psilocybin boosts the connectivity between brain regions involved in sensory and somatomotor functions, while reducing connectivity within higher-level associative networks like the Default Mode Network (DMN) (Preller et al. 2018, 2020). DMN is a highly active intrinsic network that remains highly active during restful, task-free periods when the mind is awake but not engaged in focused mental activities (Buckner et al. 2008; Raichle 2015). The medial prefrontal cortex plays a key role in executive function, attention, sensory integration, and decision-making (Diamond 2013). The posterior cingulate cortex, precuneus, and angular gyrus are key components of DMN. Altered connectivity within DMN,

especially involving hyperactivation of the medial prefrontal cortex (mPFC) alongside increased amygdala activity, has been observed in individuals suffering from major depressive disorder (MDD) (Berman et al. 2011; Coutinho et al. 2016; Lee and Roth 2012). Carhart-Harris et al. found that psilocybin reduces blood flow in several brain regions, including the medial prefrontal cortex, thalamus, anterior cingulate cortex (ACC), and posterior cingulate cortex (PCC) (Carhart-Harris et al. 2012).

Reduced blood flow in these areas corresponds to diminished neural activity and weakened functional connectivity. This indicates that psilocybin may help normalize default mode network function and reestablish typical brain connectivity in individuals with major depressive disorder (MDD). Neuroimaging research also shows that reduced connectivity within DMN is linked to impaired and maladaptive self-referential processing (Reinwald et al. 2023; Stoliker et al. 2024). These changes enhance emotional empathy (Jungwirth et al. 2025), reduce anhedonia (Stroud et al. 2018), and promote lasting personality shifts, such as lower impulsivity and neuroticism (Pagni et al. 2025). In individuals with MDD, these brain connectivity changes correlate with quick and lasting symptom relief. In contrast, SSRIs like escitalopram do not produce comparable modifications in neural connectivity (Daws et al. 2022). These results imply that psilocybin's impact on brain network activity could underlie its ability to promote lasting behavioral changes, cognitive shifts, and enhanced psychological resilience (Omidian and Omidian 2025).

6.4.4 The Cognitive and Emotional Processing

Psilocybin can induce a state where usual cognitive boundaries become less distinct, potentially enabling broader associative thinking. This shift is thought to enhance creativity and foster innovative problem-solving skills (Bonnieux et al. 2023; Mason et al. 2019, 2021). Participants in psilocybin research frequently describe heightened emotional openness, improved mood, and greater overall life satisfaction—effects that can persist for several months following just one dose (Nayak et al. 2023).

These lasting effects are believed to stem from profound, introspective experiences triggered by psilocybin, which encourage individuals to reassess their values and behaviors and work through previous traumas (Min et al. 2024). The observed alterations in brain connectivity are thought to support the enduring enhancements in mood and cognitive abilities seen after psilocybin use. Additionally, psilocybin has been found to notably decrease cognitive patterns associated with depression, such as rumination and the suppression of thoughts (Barba et al. 2022).

These effects were linked to ego dissolution and psychological insight, underscoring psilocybin's ability to enhance emotional flexibility. Furthermore, psilocybin impacts socio-emotional processing. A randomized controlled trial showed that just one dose of psilocybin significantly enhances emotional empathy toward positive stimuli in people with depression, with these improvements lasting for at least 2 weeks. These results indicate that psilocybin may enhance social cognition,

particularly benefiting individuals experiencing social withdrawal or emotional numbness (Jungwirth et al. 2025). Furthermore, Gramling et al. showed that psilocybin can improve psychotherapeutic outcomes by strengthening both verbal and nonverbal connection and engagement between therapists and patients. Their study also highlights the possibility of systematically assessing these therapeutic interactions within psychedelic treatment settings (Gramling et al. 2023).

6.4.5 Neuroplasticity

Structural neuroplasticity is known to be the main mechanism of antidepressants in the frontal cortex, whereas synaptic loss is commonly seen in the prefrontal cortex of people with depression (Barrett et al. 2020; Holmes et al. 2019). In chronic stress models, synaptic deficits such as reduced dendritic branching, decreased spine density, and impaired neurotransmission has been noted in the frontal cortex (Cook and Wellman 2004; Liston et al. 2006; Radley et al. 2004; Yuen et al. 2012). Stimulating 5-HT2A receptors on prefrontal cortex pyramidal neurons leads to heightened glutamate release and activity (Vollenweider and Kometer 2010), leading to glutamate interactions with receptors on cortical pyramidal neurons. Additionally, it has been shown to influence the creation of BDNF (Catlow et al. 2013; Ly et al. 2018). Increased neurogenesis causes the limitation of conditioned fear-related behaviors (Catlow et al. 2013). Psilocin's potential therapeutic effects, such as antidepressant and anxiolytic actions, likely stem from a complex interplay between serotonergic and glutamatergic systems in prefrontal brain circuits (Mithoefer et al. 2016; Zamaria 2014). Research revealed that a single psilocybin dose promotes dendritic spine growth in the medial frontal cortex of mice. The enduring nature of these neural changes is significant and may explain psilocybin's therapeutic effects. By restoring neuronal connectivity, psilocybin may address synaptic deficits, providing a biological basis for easing depressive symptoms (Shao et al. 2021). Additionally, this structural remodeling supports learning processes and helps in the formation and retention of long-term memories (Xu et al. 2009; Yang et al. 2009). Psilocybin-driven neural plasticity improves the brain's capacity to absorb and incorporate new psychological experiences. The neuroplastic effects of psychedelics are suggested to provide therapeutic benefits independent of their hallucinogenic properties (Peters and Olson 2021).

6.4.6 The Role of the Amygdala

The amygdala plays a key role in processing and perceiving emotions (Mahapatra and Gupta 2017). Increased amygdala reactivity leads to a higher focus on negative environmental or social stimuli, blocking the impressive processing of positive information (Disner et al. 2011). Neuroimaging shows that people with depression have increased amygdala response to fearful faces, which typically decreases after SSRI treatment (Ma 2015). Some studies suggested increased amygdala reactivity due to the

administration of psilocybin to depressive treatment-resistant patients and a reduction in the connectivity of the amygdala and prefrontal cortex (Mertens et al. 2020; Roseman et al. 2018). However, these findings contrast with other studies showing that acute psilocybin administration leads to reduced amygdala reactivity during emotional processing, suggesting variability in its effects depending on dose, timing, or individual patient characteristics (Kraehenmann et al. 2015). Kraehenmann et al. have demonstrated that psilocybin can lower amygdala activation in response to negative visual stimuli by attenuating threat signaling from the amygdala to the visual cortex, and reduce the amygdala blood oxygen level-dependent signal, which is correlated with an increase in positive mood in healthy individuals (Kraehenmann et al. 2015, 2016).

Carhart-Harris et al. (2017) observed that psilocybin reduced amygdala blood flow, linked to less depression and improved DMN connectivity. The discrepancies between study findings may stem from differences in study populations—specifically, comparisons between healthy individuals and patients with depression. Additionally, the timing of post-administration assessments relative to when psilocybin was administered could significantly influence observed outcomes.

6.4.7 Anti-Inflammatory Effects

An inflammatory state marked by elevated levels of pro-inflammatory cytokines—particularly tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6)—has been closely linked to the pathophysiology of depression, notably contributing to core symptoms such as anhedonia (Berthold-Losleben and Himmerich 2008; Bob et al. 2010; Dowlati et al. 2010; Lee et al. 2021; Ling et al. 2022; Rosenblat et al. 2014; Ting et al. 2020). Studies have shown that activation of the 5-HT2A receptors leads to downstream suppression of TNF-α and a reduction in IL-6 release in mice (Nau Jr et al. 2013). Furthermore, psychedelics like LSD, Dimethyltryptamine (DMT), and psilocybin activate 5-HT2A receptors, lowering pro-inflammatory cytokines like TNF-α and IL-6 (Dos Santos et al. 2016; House et al. 1994; Szabo et al. 2014). IL-6 directly triggers C-reactive protein (CRP) production in the liver, making CRP a key clinical biomarker of inflammation. Research shows that TNF-α levels drop rapidly after psilocybin intake but return to normal within a week. In contrast, IL-6 and CRP levels stay lowered, indicating a lasting anti-inflammatory effect that aligns with ongoing mood enhancement and increased prosocial behavior (Mason et al. 2023).

TNF-α strongly activates the kynurenine pathway, which breaks down tryptophan into kynurenine, reducing tryptophan's availability for serotonin production. This decrease in serotonin contributes to depressive symptoms. Importantly, certain metabolites of the kynurenine pathway, like quinolinic acid, are neurotoxic and have been linked to neurodegeneration and the development of depression. By influencing this pathway, psilocybin may decrease toxic kynurenine metabolites and neuroinflammation, which could help relieve depressive symptoms (Prouzeau et al. 2022). These findings suggest psilocybin's antidepressant effects stem from 5-HT2A receptor activation, which reduces pro-inflammatory cytokines TNF-α and IL-6.

6.5 Challenges and Future Directions

Psychedelic-assisted therapy shows promise for anxiety, depression, and existential distress in terminal illness, with good tolerability but low certainty of evidence. Given the legal restrictions in many countries, including the Schedule I classification by the US DEA, research is limited but growing. Future studies should address issues such as expectation bias and unblinding, and include larger sample sizes to enhance reliability (Schipper et al. 2024). Phytochemicals from medicinal mushrooms offer a promising natural source for developing new antidepressant drugs, especially considering the limitations of current medications. However, most studies are still preclinical, with challenges such as the blood–brain barrier hindering effective delivery. Research on the electrophysiological impact of these compounds on mood-related brain circuits is also limited. Although nine mushroom species have shown potential in animal and small human studies, large-scale, placebo-controlled clinical trials are needed. Further investigation into their biochemical mechanisms and active compounds is essential before clinical application (Lew et al. 2020). Medicinal mushrooms have garnered increasing attention due to their promising therapeutic properties (Wasser 2017). With the rising demand for medicinal mushrooms, the industry must evolve to harness new opportunities effectively (Chang and Buswell 2023). Future research should prioritize isolating key active compounds, refining extraction techniques, and advancing delivery systems to maximize therapeutic effectiveness (Lew et al. 2020).

Developing medicinal mushroom-based products continues to face several challenges, including the lack of standardized formulations, unresolved safety concerns, and the pressing need for rigorous clinical trials to validate their efficacy and safety (Chang and Wasser 2018). Many existing studies are limited by small sample sizes and brief follow-up durations, highlighting the need for larger, long-term randomized controlled trials to more comprehensively evaluate the efficacy and safety of these treatments (Carhart-Harris and Goodwin 2017; Davis et al. 2021; Gukasyan et al. 2022; Li et al. 2024; Scala et al. 2024).

6.6 Safety Considerations

Medicinal mushrooms are gaining popularity as natural treatments for depression due to their demonstrated health benefits. These supplements are usually safe for human use, causing few or no side effects, which indicates they have a positive safety profile (Roupas et al. 2012). Safety evaluations of medicinal mushrooms have utilized methods such as DNA barcoding, metabolite analysis, and comprehensive literature reviews (VanderMolen et al. 2017). Inconsistent psilocybin levels among mushroom species and preparations create challenges for standardized dosing. Although clinical trials use synthetic psilocybin for precise administration, natural sources vary in potency, raising concerns about potential underdosing or overdosing in real-world use (Meshkat et al. 2025). While preliminary findings are promising, many existing studies lack methodological robustness, highlighting the

need for well-designed, long-term clinical trials to confirm their efficacy and safety (Jeitler et al. 2020; Wasser 2017). Additional research is essential to address unresolved questions related to safety, effectiveness, and possible interactions with other treatments (Chugh et al. 2022).

6.7 Legal and Ethical Considerations

The rapid commercialization of psilocybin has sparked ethical concerns, notably the risk of exploiting Indigenous knowledge without proper acknowledgment or benefit sharing (Bradberry et al. 2024; Gukasyan et al. 2022; Lee et al. 2024; Ricci 2025; Scala et al. 2024). Psilocybin encounters major legal and regulatory barriers, primarily due to its designation as a Schedule I substance in countries such as the United States and Canada—suggesting a strong risk of misuse and lacking accepted medical applications (Mocanu et al. 2022; Yockey and King 2021). This classification significantly restricts both clinical research and therapeutic utilization (Nutt et al. 2013). Despite growing trends of decriminalization or medical legalization in some areas, the ensuing patchwork of regulations continues to complicate widespread availability and research efforts (Mian et al. 2025; Schonholz et al. 2024). Furthermore, questions remain about the sufficiency of informed consent, especially given Psilocybin's intense psychological effects and the limited long-term safety data available. Consequently, these barriers underscore the complex environment surrounding Psilocybin's integration into mainstream medicine.

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Protective Mechanisms of Medicinal Mushrooms and Their Biomolecules Against Neurodegeneration

7

Arian Hizomi and Syed Khaja Ayaanuddin

Abstract

This chapter evaluates mushrooms' abilities to produce bioactive substances with therapeutic applications against neurodegenerative diseases. It presents a comprehensive analysis of the existing knowledge about the important molecules in mushrooms, such as polysaccharides, peptides, phenolic compounds, terpenoids, and their antioxidant, anti-inflammatory, and neuroprotective activities. Various mushroom compounds have been tested for activity against significant biological processes such as oxidative stress, neuroinflammation, and neuronal apoptosis. This chapter also highlights various effects mushroom compounds have on relevant signaling cascades, including the Nrf2/ARE and NF-κB pathways. Lastly, this chapter discusses the current preclinical and clinical evidence, along with bioavailability and pharmacokinetic issues and dosages of mushroom-derived compounds. Furthermore, the possibility that mushroom therapies may complement the treatment of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease is further discussed. To summarize, this chapter highlights several knowledge gaps, emphasizing the clinical validation of mushroom-derived compounds along with the critical examination of the specific underlying molecular mechanisms with multidisciplinary approaches related to pharmacology, neuroscience, and molecular biology. The collective investigation of the existing literature suggests that mushrooms have great potential for neurodegenerative disease treatments, which is largely overlooked at present.

Keywords

Mushrooms · Bioactive compounds · Neurodegeneration · Molecular mechanism

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7.1 Introduction

Neurodegenerative diseases (NDs) like Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS) are some of the most debilitating and pressing challenges ("pains") facing modern medicine. NDs are characterized by progressive neuronal loss, cognitive and motor impairment, and detrimental reductions in quality of life, representing an emerging public health burden (Phan et al. 2015a, b; Silva et al. 2023a, b). Despite overwhelming evidence from studies on NDs, therapies commonly available through prescriptions mainly address the symptoms of the disease rather than the underlying molecular mechanisms of disease progression. This unmet clinical need has generated increasing interest in alternative avenues of management, such as the use of natural products from medicinal mushrooms for therapeutic neuroprotection.

Medicinal mushrooms have been revered by traditional medicine systems, predominantly in East Asian cultures, for centuries. Mushrooms' bioactive molecules, such as polysaccharides, terpenoids, phenolics, and sterols, have provided modern science with valuable evidence that offers to positively influence pathways associated with neurodegenerative diseases (Martel et al. 2019; Liuzzi et al. 2023). The therapeutic properties of medicinal mushrooms derive from their ability to provide antioxidant, anti-inflammatory, neurotrophic, antiapoptotic, and microbiota-modulating properties (Khan et al. 2013; Jiang et al. 2024a, b).

The primary means through which mushrooms mediate neuroprotection is by attenuating oxidative stress. Oxidative stress occurs when reactive oxygen species (ROS) production surpasses the body's antioxidant abilities to neutralize ROS, leading to damage to cellular lipids, proteins, and DNA. Neurons are particularly sensitive to oxidative stress due to their high level of metabolic activity, and possess few protective antioxidant mechanisms. Elevated ROS levels can cause synaptic deregulatory dysfunction and mitochondrial dysfunction, leading to neuronal apoptosis, part of the processes in the etiology of AD and PD (Liuzzi et al. 2023). Promising bioscientific evidence demonstrates that extracting bioactive molecules from mushroom species such as *Ganoderma lucidum*, *Pleurotus giganteus*, and *Hericium erinaceus* have strong antioxidant properties such as polysaccharides and ergothioneine, which have activity to scavenge ROS, upregulate endogenous superoxide dismutase (SOD) and catalase antioxidant enzymes, and reduce damaging oxidative stress to neuronal structures (Sun et al. 2017a, b; Silva et al. 2023a, b).

Neuroinflammation is another pathway mediated by mushrooms and their bioactive properties. Neuroinflammation is a chronic process driven by activated microglia and astrocytes and the release of destructive pro-inflammatory cytokines such as interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), as well as the more recently recognized activation of nuclear factor kappa B (NF-κB) pathways leading to neuronal injury and disease progression (Abitbol et al. 2022). Mushrooms have been shown to mediate neuroinflammation through their β-glucans and triterpenoids, which inhibit NF-κB activation and cytokine production; for example, the G. lucidum from mushroom-derived extracts effectively suppresses inflammatory gene expression, also shown to reduce microglia activation and can ultimately

reduce the cycle of inflammation-mediated neurotoxicity (Sun et al. 2017a, b). Mitochondrial dysfunction is another major target in neurodegenerative diseases. Mitochondria are essential to our ability to synthesize and produce energy. Like in skeletal muscle, functional mitochondria also play critical roles in regulating pro-apoptotic pathways. Dysfunction results in both depletion of ATP and heightened production of reactive oxygen species (ROS) and promotes the activation of cell death cascades. The polysaccharides and other secondary metabolites from mushrooms assist in stabilizing mitochondrial membranes, support ATP synthesis, and inhibit cytochrome c release, which is a primary mediator of apoptosis (Martel et al. 2019; Jiang et al. 2024a, b). Following their administration in AD and PD models, *H. erinaceus* and *G. lucidum* preserved mitochondrial and overall neural health (Sun et al. 2017a, b; Liuzzi et al. 2023).

Another particularly exciting area of mushroom-based neuroprotection involves their ability to enhance and/or stimulate neurotrophic factor production. Neurotrophic factors such as NGF and brain-derived neurotrophic factor (BDNF) are vital to neuronal survival, differentiation, and plasticity. Reduction of neurotrophic factors is a feature of neurodegenerative disease. The polysaccharides and other secondary metabolites from mushrooms help stabilize mitochondrial membranes, support ATP synthesis, and inhibit cytochrome c release, which is a primary mediator of apoptosis (Martel et al. 2019; Jiang et al. 2024a, b). Following their administration in AD and PD models, *H. erinaceus* and *G. lucidum* preserved mitochondrial and overall neural health (Sun et al. 2017a, b; Liuzzi et al. 2023).

Compounds from *H. erinaceus*, particularly erinacine and hericenone, have been demonstrated to promote the synthesis of nerve growth factor (NGF), induce neurite outgrowth, and enhance synaptic connectivity (Mori et al. 2009a, b; Szućko-Kociuba et al. 2023). *H. erinaceus* administration has improved cognitive ability and delayed disease symptomology in preclinical and clinical trials.

Mushrooms have intrinsic pathways that promote neuronal protection and have the ability to modulate the aggregation characteristics of proteins. The aggregating processes are forming neurotoxins such as amyloid-beta (Aβ) plaques seen in AD or fibrils of alpha-synuclein as seen in PD; these processes are potential targets for neuroprotective interventions. There is evidence that demonstrates that polysaccharides from mushrooms were able to inhibit the fibrillation process of Aβ, promote the clearance of misfolded proteins in autophagy, and ultimately assist with restoring the process of proteostasis (Silva et al. 2023a, b; Jiang et al. 2024a, b).

There is also a growing and emerging area of research looking into how mushrooms may impact gut–brain axis health. The effects of the gut microbiome on brain health and inflammatory processes, such as those through immune, metabolic, or neural mechanisms, are notable. Common dysbiosis of the gut microbiome is systemic inflammation and is potentially associated with neurodegenerative diseases due to neuroinflammation supporting neurodegenerative progression. The mushroom polysaccharides could potentially act as prebiotics and may stimulate growth beneficial gut bacteria to increase short-chain fatty acids (SCFAs), such as butyric acid, reduce systemic inflammation, and improve cognitive health outcomes (Phan

et al. 2017; Silva et al. 2023a, b). Future studies may also explore potential gut-mediated neuroprotective and cognitive resilience.

Medicinal mushrooms may provide therapeutic potential in utilizing the safety profile of their administration; while the mechanism by which many synthetic pharmacological agents notoriously induce toxicity, mushrooms, when produced/prepared properly, are generally considered safe. Nevertheless, the safety of mushrooms varies significantly and is not limited to species, growing conditions, extracts, etc., which could lead to inconsistencies in mushroom-based products (Martel et al. 2019; Liuzzi et al. 2023).

Standardization-based approaches have grown rapidly and spawned identification technologies like molecular authentication, and metabolomic analysis can ameliorate many of the challenges surrounding safety, standardization, and approval toward regulation and clinical applications.

In vivo studies have reinforced the neuroprotective capacity of medicinal mushrooms. *H. erinaceus* administration improved space learning and memory in rodent models of AD while decreasing levels of amyloid deposition and had neurogenic effects in the hippocampus (Mori et al. 2009a, b; Szućko-Kociuba et al. 2023). *G. lucidum* extracts have been demonstrated to protect degenerating dopaminergic neurons in rodent models of PD, preserving functional motor capacity while markedly reducing oxidative damage (Sun et al. 2017a, b).

Systematic reviews and meta-analyses continue to support the credibility of medicinal mushrooms in neurodegenerative models. A review observing 17 studies found that polysaccharides, terpenoids, and phenolic compounds derived from mushrooms effectively improved biomarkers of oxidative stress, inflammation, and neuronal survival in preclinical models (Silva et al. 2023a, b; Rai et al. 2021). The current findings warrant investigation in larger controlled clinical trials to verify the observed positive effects in clinical outcome measures that are relevant in therapy.

In summary, it is readily apparent that medicinal, as well as other mushrooms, provide neuroprotective properties, and unexplored compounds that can modulate multiple pathways in various neurodegenerative diseases. The unique antioxidative, anti-inflammatory, mitochondrial protective, neurogenic, and microbiota-modulating properties of medicinal mushrooms render them strong options for integrative and holistic approaches to neurodegenerative diseases. Future work should focus on clinical standardization, bioavailability, as well as mechanistic pathways to realize the true therapeutic potential of these unique fungi.

7.2 Molecular Mechanisms Implicated in Neurodegeneration and the Therapeutic Potential of Medicinal Mushrooms

7.2.1 Oxidative Stress and Mitochondrial Dysfunction

There has been extensive research on oxidative stress, and it is one of the most significant mechanisms of neurodegeneration. Oxidative stress occurs when the

accumulation of reactive oxygen species (ROS) surpasses the cellular antioxidant capacity, ultimately damaging DNA lipids, and proteins within neurons. Neurons are particularly vulnerable to oxidative stress since neurons have a high resting oxygen consumption and are made up of lipid-rich cell membranes.

Mitochondrial dysfunction is often the cause of oxidative stress in many neurodegenerative disorders (NDs). Damaged mitochondria will produce too many ROS, leading to reduced energy (ATP) production and apoptosis of neurons. Mitochondrial dysfunction occurs mainly in Alzheimer's disease (AD) and Parkinson's disease (PD), where we observe a reduction in complex activity and poor mitochondrial dynamics (Jiang et al. 2024a, b).

Medicinal mushrooms, including *H. Erinaceus* and *G. Lucidum*, have been shown to increase the associated oxidative damage. Aaronicines, Phenolics, and Ergothioneine are some of the effective ROS scavengers that support healthy mitochondrial function (Liuzzi et al. 2023).

7.2.2 Neuroinflammation and NLRP3 Inflammation

Chronic neuroinflammation is an apparent and harmful characteristic of neurodegeneration. Microglia, the immune cells of the brain, are activated chronically and release pro-inflammatory cytokines (e.g., IL-1β, TNF-α) that damage neurons.

The inflammasome NLRP3 is a key marker of this process and is important mainly in diseases like AD and MS. When NLRP3 is activated, pro-caspase-1 is cleaved into active caspase-1, which activates IL-1β and IL-18, resulting in neuroinflammation and apoptosis (Abitbol et al. 2022).

Many mushroom-derived compounds are anti-inflammatory in nature. For example, *G. lucidum* and *P. giganteus* obtained plasmids by downregulating the expression of NLRP3 and cytokines in a cascade that reduced inflammation-induced neuronal death (Sun et al. 2017a, b; Rai et al. 2021).

7.2.3 Protein Misfolding and Aggregation

The aggregation of misfolded proteins is the most common molecular manifestation of many NDs.
In AD: β-amyloid (Aβ) plaques and hyperphosphorylated tau tangles
In PD: α-synuclein Lewy inclusions
In HD: mutant huntingtin aggregates

These proteins, and their aggregates, can become unfolded aggregates that breach cell membrane integrity, disrupt cellular proteostasis, and activate apoptotic cellular pathways.

Multiple mushroom-derived molecules, including hericenones, polysaccharides, inhibit the aggregation of β-amyloid, AChE inhibitors, inhibit tau hyperphosphorylation, and facilitate autophagic and proteasomal pathways of degradation to clear away the misfolded protein aggregates (Silva et al. 2023a, b; Jiang et al. 2024a, b).

7.2.4 Cholinergic Dysfunction and Synaptic Failure

Cognitive dysfunction in AD is the outcome of cholinergic loss due to a lack of acetylcholine from cholinergic neurons in the basal forebrain. The mechanism of action for current AD treatments is based on the use of AChE inhibitors to increase the action of acetylcholine.

Several mushroom extracts, such as *H. erinaceus*, have been shown to exhibit AChE inhibitory activity and increased cholinergic function (Phan et al. 2015a, b; Mori et al. 2009a, b). In addition to this activity, these compounds can increase the synthesis and release of neurotransmitters and induce synaptic plasticity.

7.2.5 Apoptosis and Neuronal Death

Apoptosis (programmed cell death) is downstream of several of the mechanisms previously detailed, with mitochondrial dysfunction, ROS load and inflammatory cytokines all converge into the apoptotic cellular pathway, which typically include cytochrome c release, initiation of caspases (notably caspase-3), and upregulation of pro-apoptotic proteins such as Bax and Bim. Mushroom polysaccharides and triterpenes influence anti-apoptosis by regulating apoptosis-related genes. For example, the polysaccharides of *G. lucidum* increase Bcl-2 expression and decrease caspase-3 activity (Sun et al. 2017a, b; Hassan et al. 2022a, b).

7.2.6 Excitotoxicity and Calcium Imbalance

Glutamate excitotoxicity happens when an excess of glutamate leads to overstimulation of NMDA receptors, consequently elevating intracellular calcium levels, mitochondrial overload, and subsequent neuronal cell death. This mechanism is especially notable in ALS and ischemic injury.

Bioactive constituents from mushrooms, including antioxidants and metal chelators, can help maintain calcium homeostasis while reducing excitotoxicity induced by glutamate (Yadav et al. 2020).

7.2.7 Impaired Neurotrophic Signaling

Neurotrophic factors, neuronal growth factor (NGF), and brain-derived neurotrophic factor (BDNF), are provided to neurons to promote survival, growth, and differentiation; under normal conditions, NDs demonstrate a significant reduction in the production of these proteins.

One of the main encouraging aspects of *H. erinaceus* is its ability to stimulate the synthesis of NGF. Erinacines and hericenones have demonstrated the capacity to stimulate the regulation of genetic expression of NGF and enhance neurite

outgrowth, therefore augmenting neural regenerative abilities (Szućko-Kociuba et al. 2023; Brandalise et al. 2023).

Synergistic Effects of Mushroom Bioactives for Neurodegeneration
Medicinal mushrooms can provide multi-targeted therapeutic capacity, which can be advantageous in undertaking the multifactorial pathophysiology of NDs. As described, medicinal mushrooms can modulate individual pathways, yet interact in unison:
Antioxidant + anti-inflammatory (reduce the oxidized radicals and cytokine storm)
Neurotrophic + antiapoptotic (cell survival)
Anticholinesterase + synaptogenic (cognition)

Moreover, they have low toxicity, are natural, and may be of potential value as a dietary supplement, especially for chronic condition use in both prevention and therapy (Venturella et al. 2021a, b).

7.2.8 Autophagic Inefficiency and Impaired Protein Clearance

Within the cellular metabolism, autophagy serves a vital role in the clearance of damaged organelles and misfolded proteins, which is particularly important to long-term and post-mitotically activated cells (i.e., neurons). Autophagy pathobiology is dependent upon the similar fundamental aspects of astrocytes in the nervous system; hence, a problem with autophagic flux is also an inflow of accumulation of misfolded toxic proteins, such as β-amyloid (Aβ) in Alzheimer's disease and alpha-synuclein in Parkinson's disease (Martel et al. 2019). Although, a notable component of autophagy dysregulation is also the proximal events surrounding neuroinflammation, low energy, and cell death related to the perceived limitations of the autophagy-lysosome pathway.

Mushrooms, in particular *G. lucidum*, have reportedly demonstrated a mechanistic ability to induce autophagy by signaling AMPK/mTOR and PI3K-Akt pathways (Lee et al. 2019). Collectively, these complex cell-signaling pathways are responsible for the adequate initiation of autophagy and the requisite lysosomal degradation of damaged vesicles. Moreover, triterpenoids of fungi stimulate lysosome biogenesis and promote intracellular clearance (Hassan et al. 2022a, b).

7.2.9 Endoplasmic Reticulum (ER) Stress and Unfolded Protein Response

The endoplasmic reticulum (ER) undergoes the events related to ER stress, which is caused by the accumulation of misfolded proteins in the ER that activate the unfolded protein response (UPR). Subsequently, UPR can activate apoptosis triggered by CHOP and JNK, especially when exposed to chronic ER stress in the pathways surrounding AD, PD, and ALS (Jiang et al. 2024a, b).

Bioactive constituents from mushrooms, particularly those belonging to *H. erinaceus*, exhibit a capacious impact to reduce ER stress through diminution of oxidative radical species and restoration of calcium homeostasis within the ER lumen (Szućko-Kociuba et al. 2023). Further, ergothioneine and hericenones modulate BiP and PERK expression, thereby contributing to UPR downregulation and improving the protein folding ability of the polysomal complexes (Li et al. 2023).

7.2.10 Mitochondrial Biogenesis and Energy Metabolism Regulation

Mitochondrial quality control and biogenesis are now recognized as important therapeutic targets in addition to oxidative stress. Adequate mitochondrial turnover can maintain a healthy population of neurons capable of meeting energetic demands.

Terpenoids and polysaccharide products obtained from mushrooms improve mitochondrial membrane potential and increase ATP production by upregulating PGC-1α and NRF1/2 (transcription factors inducing mitochondrial biogenesis) (Phan et al. 2015a, b; Yadav et al. 2020). This not only supports neuronal survival but also diminishes fatigue and cognitive changes due to neurodegeneration.

7.2.11 Epigenetic Regulation and Neuroplasticity

Recent literature has identified newer epigenetic modifications in the family of epigenetics responsible for regulating genes involved in synaptic plasticity, memory, and resilience (i.e., histone acetylation and DNA methylation), suggesting their role in cognition is still developing.

Khan et al. (2013) found that natural products, including fungal-derived products, have the potential to modulate HDACs and DNMT activity and reestablish gene expression for neuroplasticity. Especially polysaccharides such as β-glucans derived from mushrooms can also modulate histone deacetylases and upregulate BDNF and NGF, which is proposed to be a key mechanism for the restoration of cognition and stabilization of mood (Sabaratnam et al. 2013).

7.2.12 Gut–Brain Axis and Microbiota–Neuroimmune Interactions

The role of the gut–brain axis as a neurodegenerative risk factor is currently gaining recognition, and microbial dysbiosis is implicated as a contributory risk factor related to systemic inflammation and neurotoxicity. Dysregulated flora of the gut has the potential to impact the metabolic phenomenon of tryptophan, barrier permeability, and SCFA as prerequisites to proper brain function.

Mushrooms containing high levels of polysaccharides can act as prebiotics to promote beneficial gut microbiota and diminish pro-inflammatory microbiota

(Venturella et al. 2021a, b). This also increased the production of SCFAs (e.g., butyrate) that have anti-inflammatory properties in both the gut and CNS. Additionally, ergothioneine found in mushrooms can cross the blood–brain barrier to protect against oxidative damage from gut inflammation (Contato & Conte-Junior, 2025a, b).

7.2.13 Metal Ion Dysregulation and Chelation

Metal ions (i.e., iron, copper, zinc) are essential components of oxidative chemistry and often become dysregulated in the AD condition, where they catalyze Fenton reactions that produce reactive oxygen species. Iron accumulation is particularly associated with neuronal cell death and cognitive deficits.

Some edible mushrooms produce natural metal-chelating agents (e.g., phenolics, flavonoids, polysaccharide-protein complex) that have been shown to inhibit the metal-induced aggregation of amyloid beta and protect against iron or copper-mediated oxidative injury (Kozarski et al. 2015; Jiang et al. 2022).

7.2.14 Myelin Degeneration and Support of Oligodendrocytes

The degeneration of oligodendrocytes causes impaired axonal conduction and neuroinflammation that mediates both multiple sclerosis and other demyelinating disorders. Many studies are currently supporting evidence that natural products can promote myelin repair and oligodendrocyte support.

Lanostane triterpenoids isolated from *Laetiporus sulphureus* and *Antrodia* sp. have been shown to mediate NGF production and promote the growth and survival of oligodendrocyte nuclei and neurites (Hassan et al. 2022a, b). This was shown to be an important step for the remyelination process and ultimately restore functional neural circuits associated with the degeneration of these conditions.

7.2.15 Neurogenesis and Adult Brain Plasticity

Neurogenesis, particularly in the hippocampus is critical for memory and mood. Neurogenic niches would be diminished with age and neurodegeneration and have an associated chronic inflammation and reduction in neurotrophins.

Mushroom extracts have been shown to have pro-neurogenic effects such as reducing chronic neuroinflammation, decreasing chronic neuroinflammation, increasing cell proliferation in the hippocampus, and even increasing dendritic complexity. For example, *H. erinaceus* induced the proliferation of neural stem cells and synaptogenesis in substrates enriched with NGF and BDNF neurotrophins activity, which correspondingly improved performance in spatial learning/memory tasks in aged and in disease models (Brandalise et al. 2023; Mori et al. 2009a, b).

7.2.16 Blood–Brain Barrier (BBB) Integrity and Neurovascular Health

The BBB is compromised when peripheral toxins and inflammatory mediators enter the brain, causing a worsening of neuronal injury. As such, preserving BBB integrity is an important step to halt a neurodegenerative process.

Mushroom bioactives such as ergosterol and triterpenoids have been shown to strengthen the tight junctions of endothelial cells and inhibit matrix metalloproteinases, both of which have been associated with BBB breakdown (Martel et al. 2019). This is also helpful in promoting neuroprotection along with a decreased influx of peripheral immune cells into the brain parenchyma.

7.3 Neuroprotection Mechanisms of Mushrooms and Their Bioactive Components

Neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis are marked by progressive neuronal dysfunction, synaptic loss, and, ultimately, cell death. No effective cure has been identified despite many years of research, and therapies remain only successful in ameliorating symptoms. In this light, naturally derived products are gaining attention that may protect from neurodegeneration by influencing multiple biological pathways simultaneously.

Across nature, medicinal mushrooms have been established as a powerful source of neuroprotective agents, possessing functions relating to antioxidant, anti-inflammatory, immunomodulatory, and neuroregenerative properties. Previous literature provides evidence that medicinal mushrooms have been utilized in Eastern health systems, and importantly, bioactive properties are recognized scientifically regarding their potential, including polysaccharides, phenolic compounds, terpenoids, and specific secondary metabolites such as hericenones and erinacines (Kozarski et al. 2015). These compounds express multimodal activity in preclinical and clinical studies. The compound activities support neural homeostasis, improved cognitive functioning, and modulation of molecular pathways involved in neurodegeneration.

The neuroprotective functions of mushrooms are not linked to a singular mechanism but a collaborative action of biological activity makes them attractive for neurodegenerative diseases and syndromes affecting the same systems. This chapter explores mushrooms' neuroprotection mechanisms. The authors stratified the evidence from the existing literature into four primary subcategories: antioxidant properties, anti-inflammatory effects, cognitive enhancement and neurogenesis, immunomodulation and epigenetic regulation. Each protective mechanism is supported by references drawn exclusively from peer-reviewed research supplied within the reference set.

7.3.1 Antioxidant Properties

The cerebral landscape is highly vulnerable to oxidative damage due to high consumption rates of oxygen and rich fat content. ROS are a fundamental player in the underlying mechanisms associated with the pathogenesis of multiple neurodegenerative disorders: Alzheimer's disease, Parkinson's disease, etc. Bioactive components from medicinal mushrooms have shown to positively influence antioxidant protective properties and mechanism indicating their function in neuroprotection is vital.

H. erinaceus, or Lion's Mane, has been a major focus of antioxidant potential research among multiple medicinal mushroom species. Different methods of cultivation and processing methods impact the antioxidant activities of *H. erinaceus* indicating bioactive metabolites of an organism responding to environmental conditions. Overall, *H. erinaceus* extracts revealed high free radical scavenging activity, which contribute for cellular protection from oxidative stress.

Additionally, the mechanisms for mushroom's antioxidant activity may very well be contingent upon phenolic compounds, polysaccharides, and terpenoids; these same agents may also bolster a response from endogenous antioxidant signaling systems (superoxide dismutase (SOD), catalase, and glutathione peroxidase) or directly interacting with free radicals (Wasser 2002). Beta-glucans, a type of polysaccharides found in many mushroom species, have been linked to modifying redox balance and reducing oxidative neuronal injury (Wasser 2002).

The importance of antioxidants in neurodegenerative diseases also includes the inability to prevent lipid peroxidation and protein oxidation in neuronal tissue. Both in vitro and in vivo studies have provided evidence for these neuroprotective effects, with mushroom-derived antioxidants preserving mitochondrial function and apoptotic cell death in neural cells (Khan et al. 2013). Thus, mushrooms can be considered a natural source of antioxidant compounds that can prevent or delay the initiation of neurodegenerative disorders by decreasing oxidative stress (Khan et al. 2013).

7.3.2 Anti-Inflammatory Effects

Chronic neuroinflammation is a common feature of neurodegenerative diseases and leads to neuronal dysfunction and activation, leading to a death phase. Mushroom bioactives have been demonstrated to have anti-inflammatory effects and produce effects in food also are shown to suppress pro-inflammatory mediator production and modulate immune responses.

The inflammatory pathway in the central nervous system (CNS) includes cytokines such as TNF-α, IL-1β, and IL-6, which are produced from activated microglia. The ability of medicinal mushrooms has been demonstrated as products derived from mushrooms often inhibit these cytokines, leading to inflammation-mediated damages. Research studies have shown that polysaccharides derived from mushrooms such as *G. lucidum* and *H. erinaceus* likely share similar mechanisms of

action in inhibiting microglial activation and intermediates of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) (Wasser 2002).

Anti-inflammatory pathways also target signaling pathways such as NF-κB and MAPK signaling pathways as part of the action of medicinal mushrooms that target the regulation and transcription of inflammatory genes. Naturally derived compounds such as those in mushrooms also inhibit the phosphorylation and degradation of IκB, thereby inhibiting NF-κB translocation to the nucleus, leading to downregulation of the transcription of pro-inflammatory mediators (Khan et al. 2013). This creates a neuroprotective milieu with downregulated cascades that become regulated in inflammatory responses to create a more responsive and non-reactive anti-inflammatory response.

Furthermore, CNS health can be benefited by the presence of bioactives in mushrooms as they help suppress systemic inflammation (however, indirectly). Since peripheral inflammatory markers can also regulate or signal to CNS health and behaviors (facilitated across the blood-brain barrier), an action such as a mushroom product will assist in alleviating peripheral inflammation, thus preserving the functional integrity of the neurovascular unit and reducing associated neuroinflammatory responses (Wasser 2002).

Mushrooms contain ergothioneine, a sulfur-containing antioxidant, and therefore, potential direct anti-inflammatory actions from the sulfur compounds in mushrooms that inhibit pro-inflammatory cytokines, a research study has demonstrated that ergothioneine protects neurons from inflammation and associated damage which ergothioneine mechanism of action is also shared through potentially antioxidant pathways (Khan et al. 2013).

7.3.3 Neurogenesis and Cognitive Enhancement

From the neuroprotective perspective of mushroom therapeutics, one potential effect is the improvement of neurogenesis and cognition. Neurogenesis is the creation of neurons, and this underlies learning, memorizing, and healing from an injury inside the human brain. *H. erinaceus* has been the focus of research because of its neurotrophic properties. In a clinical study, it was clinically demonstrated that oral consumption of *H. erinaceus* produced significant improvement in mild cognitive impairment in seniors (Mori et al. 2009a, b). This improvement was attributed to *H. erinaceus* increasing the synthesis of nerve growth factor (NGF), a neurotrophin, which is well-characterized for the growth, maintenance, and survival of neurons (Mori et al. 2009a, b). In animal models of NGF supplementation, *H. erinaceus* extract promoted neurogenesis in the hippocampus, increased recall memory, and improved spatial recognition, indicating preventive and therapeutic effects on cognitive impairment. Intriguingly, bioactive compounds erinacines and hericenones isolated from the mushroom were demonstrated to cross the blood–brain barrier, and they stimulated NGF synthesis in the brain (Mori et al. 2009a, b). Thus, mushroom cognitive improvement is by no means NGF stimulation only. Several bioactive compounds in the mushrooms can alter acetylcholine and cholinergic

transmission, both needed for memory and attention. By adjusting neurotransmitter levels, mushrooms might help neurons of the cholinergic system and thus give rise to a range of neurological benefits. Thus, a prolonged dietary supplementation with neurotrophic mushrooms might act as a preventive measure against cognitive decline. Overall, these data indicate the therapeutic utility of mushrooms in general and that they can be functional foods for promoting cognitive longevity (Mori et al. 2009a, b).

7.3.4 Immunomodulation and Epigenetic Regulation

Neuroprotection is composed of mechanisms that include immune function modulation and reshaping of the epigenetic landscape of the neuronal cells, as exemplified by immunomodulatory activity through mushrooms. Depending on their nature and action, these mushrooms can stimulate or downregulate immunological pathways, either innate or adaptive, for that matter, to prevent the onset of symptomatology from the slowly moving neurodegenerative disease.

Polysaccharides, specifically beta-glucans from fungi, can act as biological response modifiers (BRMs) to stimulate the function of immune cells such as macrophages, natural killer (NK) cells, and T-lymphocytes to improve neuroinflammatory responses and maintain neuronal integrity (Wasser 2002). The immunomodulatory action of mushrooms is essential to reset dysregulated immune functions, which are prevalent in neurodegenerative types of diseases.

Epigenetic regulation, which alters gene expression by intervening in DNA methylation, histone modification, and noncoding RNAs, has recently emerged as a key mechanism in neurodegeneration. Various forms of natural products derived from mushrooms have shown epigenetic activity, including the ability to inhibit histone deacetylases (HDACs) and also alter microRNA expression. Inhibiting HDAC can upregulate genes with neuroprotective roles and downregulate those genes with pro-inflammatory functions (Khan et al. 2013).

This capability to simultaneously alter immune functioning and gene expression patterns places these mushrooms on a unique path to neurotherapeutics. For example, compounds extracted from mushrooms may be able to activate the Nrf2 pathway, which causes a direct upregulation in the expression of antioxidant or detoxification-related genes via epigenetic mechanisms (Khan et al. 2013). The changes in gene expression are heritable in memory but completely reversible in function, potentially allowing for a distinctly phenomenal target for promoting long-term neuroprotection.

The combined immunomodulatory and epigenetic effects provide a way in which mushrooms can work synergistically against complex classes of neurological diseases. Therefore, medicinal mushrooms could be a valuable source of compounds, not only to protect neurons from damage, but in reprogramming the environment of the cell for repair and survival.

7.4 Conclusion

Neuroprotective mechanisms of mushrooms are diverse, potent, and well-evidenced by scientific literature. From the perspective of antioxidative defense, anti-inflammatory functions, promotion of neurogenesis, and modulation of immune or epigenetic pathways, mushrooms and their bioactive constituents offer a convincing natural course for the prevention and treatment of neurodegenerative disease. More studies and clinical validation are, therefore, needed to incorporate these compounds into a therapeutic regimen. Nonetheless, there is enough evidence so far to consider mushrooms as, both in dietary and pharmaceutical forms, potent neuroprotectants.

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Therapeutic Potential of Medicinal Mushrooms on Alzheimer's Disease

8

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Abstract

Millions of people lose their memories together with independence and quality of life because of Alzheimer's disease (AD), which is a destructive neurodegenerative disorder. The absence of any effective treatment for this disease has driven scientists to discover new therapies through medicinal mushrooms. The mushrooms *Hericium erinaceus* (Lion's Mane), *Ganoderma lucidum* (Reishi), and *Cordyceps* spp. demonstrate potential as AD game changers because they contain neuroprotective compounds. These fungi have dual benefits for brain health because they directly target neurodegenerative mechanisms, which reduce beta-amyloid plaques and tau tangles and reduce neuroinflammatory turbulence. The psychedelic compound psilocybin found in particular mushrooms demonstrates potential benefits for mood improvement and cognitive function and neuroplasticity enhancement, which slow down the progression of AD. The ancient natural remedies present an opportunity to establish a new generation of Alzheimer's treatments. The review explores the remarkable field of medicinal mushrooms and their potential to serve as transformative therapy for this major medical issue of our time.

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Keywords

Cognitive stimulation therapy · Memory enhancement · Executive function · Neuroplasticity · Cognitive rehabilitation

8.1 Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative condition characterized by cognitive decline and behavioral abnormalities, which include impaired memory, speech comprehension, attention span, reasoning capacity, executive functions, and an increase in aggressive behavior. Over time, an individual's capacity to perform normal daily tasks significantly declines, causing dependency and ultimately progressing to death. An early-onset Alzheimer's disease (EOAD) is characterized by more aggressive progression in cognitive functional decline. The development of biomarkers, including neuroimaging indicators derived from amyloid and tau PET scans, cerebrospinal fluid (CSF), and plasma markers like amyloid, tau, and phospho-tau levels, has significantly advanced the diagnosis of EOAD (Kumar et al. 2024).

The central hallmark of AD pathogenesis is an intracellular and extracellular accumulation of neuritic plaques, which consist of aggregated amyloid-beta proteins and neurofibrillary tangles composed of tau proteins (Yarns et al. 2022). Amyloid-beta and tau aggregates cause neuronal damage inducing inflammation and extracellular accumulation, impairing synaptic transmission, and leading to disruption in cholinergic signaling pathways manifested in memory loss and impaired cognitive functions. Chronic neuroinflammation, overactivation of microglia and astrocytes, inflammatory cytokine release, and oxidative stress by the production of reactive oxygen disease, such as superoxide anion radical and hydroxyl radical, have all been implicated in the pathogenesis of the disease (Silva et al. 2023). There is currently no cure for AD, and currently used medications do not halt the disease progression, only alleviate symptoms. The development of new therapeutic and preventative measures that act on different pathologic pathways is necessary (Passeri et al. 2022).

Medicinal mushrooms have been used in traditional therapies for decades. Exploring the role of active compounds derived from natural products could potentially prove beneficial for use in Alzheimer's disease as a preventive and adjunctive treatment (Silva et al. 2023). Mushrooms have been long used by humans for edible and medicinal purposes. There exist 2000 edible mushroom species out of which 270 species can be characterized as medicinal mushrooms for their therapeutic potential (Sabaratnam et al. 2013). Extracts and compounds from medicinal mushrooms such as *Hericium erinaceus*, *Antrodia camphorata*, *Ganoderma* spp., *Cordyceps* spp., and *Armillaria mellea* are characterized by their anti-inflammatory properties and have a lengthy history in traditional medicine. Medicinal mushrooms may be investigated as a potential substitute for AD treatment (Kushairi et al. 2020). For example, one of the well-known medicinal fungi, *Ganoderma lucidum*

(*G. lucidum*), has a history of being consumed through food and has bioactive components that have anti-inflammatory, antitumor, antiaging, and immunomodulatory properties. One possible treatment for AD is *G. lucidum*, which can postpone the disease and enhance cognitive performance and life quality via modification of NF-κB/MAPK signaling pathway, inhibition of neuronal death, and modulation of the immune system (Chen et al. 2024).

There are numerous health-promoting substances found in medicinal mushrooms that help to improve AD health. These include proteins, lipids, polysaccharides, terpenoids, phenols, and other bioactive molecules. Strong neuroprotective small molecules in mushrooms, including ergothioneine, erinacine, flavonoids, alkaloids, ergosterol, and melanin, are especially remarkable and should be carefully examined for their potential as a treatment for AD (*Na* (Li et al. 2023)). The production of various antioxidant compounds, including phenolics, flavonoids, polysaccharides, vitamins, carotenoids, ergothioneine, and others, has been documented in a variety of edible mushrooms. These compounds may be used as dietary supplements to strengthen antioxidant defenses and, as a result, prevent age-related neurological diseases (Liuzzi et al. 2023).

Natural products made from mushrooms have demonstrated benefits in a number of AD-related mechanisms, such as the inhibition of β-secretase (BACE 1) and acetylcholinesterase (AChE), the prevention of neurotoxicity and amyloid beta (Aβ) aggregation, the prevention of Tau expression and aggregation, and the potential for antioxidant and anti-inflammatory properties that will be discussed below (Silva et al. 2023).

8.2 The Effects of Medicinal Mushrooms on Alzheimer's Disease

8.2.1 Medicinal Mushrooms Enhance Executive Functioning, Memory, and Attention

Studies demonstrate that Lion's Mane mushroom activates NGF synthesis, which serves as a key factor for neuronal development and survival along with neuronal upkeep. The results of a double-blind placebo-controlled study indicated Lion's Mane supplements helped individuals with mild cognitive impairment improve their cognitive performance more than the placebo group, but cognitive benefits disappeared once supplement use ended (Mori et al. 2009). Prolonged medication use seems necessary for sustaining these cognitive benefits.

AD implication: Increased NGF concentrations have been found to promote synaptic plasticity as well as neuronal health thus possibly reducing the rate of cognitive deterioration in Alzheimer's disease patients (Mori et al. 2009; Wasser 2014).

Reishi serves as an adaptogenic mushroom, which helps people manage stress while this condition worsens cognitive impairment in AD patients. Preclinical experiments have found Reishi extract to improve memory function and learning capacity through its antioxidant properties and its ability to control inflammation

(Feng et al. 2019). The stress-relieving effects of Reishi on humans have not been directly tested in AD patients, yet these effects may lead to better preservation of cognitive flexibility and executive function.

Implication for AD: Through stress reduction, Reishi may support cognitive function while slowing down the worsening of AD-related cognitive impairments (Feng et al. 2019; Lindequist 2013).

8.2.2 Neurotransmitter Modulation: Chaga, *Cordyceps*, and Lion's Mane

The pathophysiology of AD significantly depends on the neurotransmitter imbalances that occur between acetylcholine and glutamate. Lion's Mane demonstrates the ability to boost cholinergic function that directly affects learning and memory processes (Mori et al. 2009). Initial research indicates Chaga (*Inonotus obliquus*) and *Cordyceps* (*Cordyceps militaris/sinensis*) may affect acetylcholine and glutamate balances yet additional research must validate these findings (Patel and Goyal 2012).

AD implication: The balance between neurotransmitters leads to better synaptic communication that benefits both global cognitive processing and certain memory problems related to AD (Xu et al. 2012).

8.2.3 Psilocybin-Containing Mushrooms and *Cordyceps*: Mood and Neurotransmission

Psilocybin functions as a serotonin receptor agonist in certain mushrooms while showing strong antidepressant effects in clinical research (Reiche et al. 2023). Since depression together with mood changes frequently occur in AD patients, psilocybin shows promise for treating mood issues through serotonin modulation.

AD implication: Psilocybin shows promise to enhance life quality alongside cognitive performance in Alzheimer's patients through its mood-improving effects (Reiche et al. 2023).

8.2.4 *Cordyceps*: Adaptogenic Properties and Dopamine Regulation

The adaptogenic nature of *Cordyceps* makes it famous together with its ability to affect dopamine systems, which help regulate mood and drive. Research on AD patients remains scarce but *Cordyceps*'s dopaminergic modulation in preclinical tests indicates its potential to boost mood and possibly enhance cognitive function (Wachtel-Galor 2011).

AD implication: Improved dopamine regulation works to stabilize mood while improving cognitive performance thus reducing some neuropsychiatric symptoms of AD (Valverde et al. 2015; Wachtel-Galor 2011).

8.3 Antioxidant and Anti-Inflammatory Properties: Neuroprotection

Neuronal damage in AD is primarily caused by oxidative stress and chronic inflammation. A number of medicinal mushrooms, such as White Button (*Agaricus bisporus*), Shiitake (*Lentinula edodes*), and Turkey Tail (*Trametes versicolor*) have mild antioxidant effects; Reishi, Lion's Mane, Chaga, and some *Cordyceps* species have strong antioxidant and anti-inflammatory activity (Friedman 2016; Roupas et al. 2012). These compounds act as neuron protectants against oxidative stress and inflammatory response, which are essential in the development of AD.

Implication for AD: It is possible that these mushrooms may help in the management of AD by reducing the oxidative stress and inflammation, thus helping in the preservation of neuronal function and slowing down the AD pathology (Friedman 2016; Xu et al. 2012).

8.4 Prevention of Beta-Amyloid and Tau Protein Deposition

Beta-amyloid plaques and tau protein tangles are considered to be the pathological features of AD. Some studies indicate that certain compounds found in Reishi and Lion's Mane may affect the process of formation or aggregation of these proteins, though the evidence is limited (Sullivan et al. 2006; Xu et al. 2012).

Implication for AD: If these mushrooms can indeed reduce the accumulation of beta-amyloid and tau proteins, then they may be useful in altering the course of AD and improving the quality of life, which is an encouraging sign for a potential therapeutic intervention (Sullivan et al. 2006; Xu et al. 2012).

8.5 Medicinal Mushrooms' Effect on Neuroplasticity and Synaptogenesis

A significant factor driving the progression of Alzheimer's disease is neuronal inflammation caused by microglial over-activation, causing cellular degeneration and halting synaptogenesis and neuronal sprouting (Peng et al., 2015). Cordycepin, an active compound derived from *Cordyceps militaris* mushroom, was added to primary hippocampal neurons that were previously treated with lipopolysaccharide conditioned medium (LP-CM), which showed enhanced neuronal sprouting and outgrowth by demonstrating increased neurite density, length, and complexity and restoration of dendritic tips and neurite length, suggesting increased neuronal connectivity (Peng et al., 2015). Another interesting finding was an upregulation in

Growth-Associated Protein 43 (GAP43) expression, a key protein driving neuroplasticity, suggesting that cordycepin can recover and reverse impairment of neuronal growth after microglial over-activation (Peng et al., 2015).

Another medicinal mushroom, *H. erinaceus*, also known as the Lion's Mane mushroom, has been extensively studied, particularly its role in neuroplasticity and cognitive functions. The mushroom contains many bioactive compounds, of which erinacines and hericenones have been shown to promote nerve growth factor gene expression and neurite outgrowth (Spelman et al. 2017). Nerve growth factor (NGF) is a neurotrophin that induces neurite outgrowth in neurons by Tropomyosin receptor Kinase-A receptor binding and signal transduction, which plays an important role in the process of synaptic plasticity and neuronal differentiation (Liu et al. 2007). *E*rinacines can cross the blood–brain barrier and directly stimulate NGF gene expression, promoting neuronal growth, differentiation, and neurite sprouting (Kawagishi et al., 2008). The binding of NGF to tropomyosin receptor kinase A (TrkA) results in the activation of Cyclic adenosine monophosphate-response element-binding protein (CREB) signaling cascade, which in addition to synaptic plasticity resulted in mitochondrial remodeling, ultimately improving its bioenergetic capacity and as a result, contributing to neurogenesis and nerve regeneration (Yanshree et al. 2022). Another independent study demonstrated that NGF stimulation by ethanol extract of *H. erinaceus* demonstrated a concentration-dependent effect on increased NGF gene expression in human astrocytoma cells, and oral supplementation of 5% *H. erinaceus* extract for 7 days to mice showed significant upregulation of NGF mRNA in the hippocampus (Mori et al. 2009). Furthermore, *H. erinaceus* fruiting body (HEFB) has been studied in mice with Alzheimer's disease, which demonstrated improved spatial and short-term memory functioning, after which the double-blind, placebo-controlled clinical trial was repeated in humans with mild cognitive impairment by administering 250 mg HE tablets (96% dry powder) three times daily for 16 weeks, which showed significant cognitive improvement on the dementia rating scale and cognitive decline after discontinuation of the tablet, suggesting that continued use of HE supplementation can be beneficial in the early stages of Alzheimer's disease (Mori et al. 2009).

8.6 Medicinal Mushrooms Effect Sleep and Circadian Rhythms in Alzheimer's Disease

Sleep disturbance is considered both a predictor for neurodegeneration and cognitive decline and a consequence of Alzheimer's disease, increasing inflammation and beta-amyloid burden (Irwin Michael and Vitiello 2019). Targeting sleep can be a preventative and therapeutic strategy for Alzheimer's disease (Mander Bryce et al. 2016). However, there is uncertainty in the effectiveness and safety profile for the use of classical hypnotics, including benzodiazepines and melatonin in Alzheimer's disease, necessitating further research on different compounds modifying sleep (Qin et al. 2024). *G. lucidum*, also known as Reishi, has been studied for its potential to be used in the treatment of Alzheimer's disease. A study conducted on animal

rat models with Alzheimer's disease exhibiting sleep disturbances— increased wakefulness and reduced NREM and REM sleep—demonstrated that G. *lucidum* extracts have moderate affinity to $GABA_A$ receptors and alleviated sleep disturbances in diseased rats (Qin et al. 2024). Another study also proved that *G. lucidum* has hypnotic effects by feeding *G. lucidum* extract to rats and assessing sleep function through electroencephalographic and electromyographic recordings, showing increased total sleep time and non-rapid eye movement (REM)sleep and no changes in slow-wave sleep and REM sleep (Cui et al. 2012). In mice experimental models, *G. lucidum* not only improved total sleep time and enhanced NREM sleep, but also influenced the gut–brain axis to promote its sleep-modifying effects (Yao et al. 2021). By altering the composition of gut microbiota, specifically increasing *Lactobacillus* and *Bifidobacterium*, *G. lucidum* increased both colon and brain serotonin concentrations by enzymatic conversion of amino acid tryptophan to serotonin, hence also increasing melatonin synthesis (Yao et al. 2021). In the same mice study, treatment with antibiotics, which also decreased microbiota, the sleep-promoting effects of *G. lucidum* disappeared, further strengthening the suggestion of the involvement of the gut–brain axis as the sleep-modulatory role of *G. lucidum* (Yao et al. 2021).

8.7 The Default Mode Network (DMN) Activity in Alzheimer's Disease and Psilocybin

The default mode network is interconnected brain regions representing resting-state baseline brain activity (Simic et al. 2014). The DMN is associated with cognitive states that are directed toward the self and include introspection, self-referential thinking, and autobiographic memory (Grieder et al. 2018). The brain regions that participate in forming a DMN network are the posterior cingulate cortex, precuneus, dorsal and ventral medial prefrontal cortex, lateral parietal cortex, and medial temporal lobes (Wang et al. 2013). In addition to cortical structures, subcortical structures are also involved in the DMN network, including the thalamus, cerebellar lobule and vermis, amygdala, and caudate nucleus (Seoane et al. 2024). DMN connectivity declines in early cognitive decline and mild cognitive impairment as well (Wang et al. 2013). DMN alterations within subcortical regions in Alzheimer's disease can serve as a potential early biomarker and include decreased functional connectivity or a left-lateralized decline in the medial temporal lobe, amygdala, and left anterior hippocampus, in addition to compensatory increased activity in the right anterior insula (Seoane et al. 2024).

Psilocybin is a naturally occurring psychedelic compound derived from the *Psilocybe* mushroom species (Van Court et al. 2022). Psilocybin has been studied for its properties to alter DMN connectivity, demonstrating disruption of integrity within the default mode network and increased connectivity of DMN with other brain networks rich in 5-HT2A receptors, leading to an increase in divergent thinking (Mason et al. 2021). Additionally, the use of psilocybin has been associated with improvement in semantic learning (Meshkat et al. 2024). One week of

administration of psilocybin showed decreased glutamate and *N*-acetylaspartate concentrations in anterior cingulate cortex, and as a result, increased functional connectivity between posterior and anterior cingulate cortical regions, leading to an increase in cognitive flexibility (Doss et al. 2021).

8.8 Medicinal Mushrooms: Ethical, Environmental, and Clinical Considerations

For many generations, medicinal mushrooms have been employed in medical practice because of their known healing properties across multiple cultures around the world (Wasser 2014). The scientific community has restarted its research into these fungi because they hold promise for various healthcare applications including oncology, immunology, and metabolic disorders (Xu et al. 2012). The growing interest in medicinal mushrooms requires a thorough evaluation of their ethical dimensions alongside environmental aspects, their clinical value, and possible drug interactions (Friedman 2016).

8.9 Wild Foraging and Conservation

Harvesting mushrooms from their natural habitats maintains traditional harvesting approaches and can yield compounds that exist exclusively in their native settings (Sullivan et al. 2006). The excessive collection of mushrooms leads to environmental hazards that decrease species diversity while damaging ecosystem functionality (Roupas et al. 2012). Unregulated mushroom collection may exhaust specific populations, which creates adverse effects on forest ecosystems and all organisms depending on fungal biodiversity (Valverde et al. 2015). Wild mushroom species require sustainable harvesting approaches for maintaining their populations and their environmental functions (Lindequist 2013).

8.10 Controlled Cultivation and Standardization

Medicinal mushrooms produced for biopharmaceutical use through standardized controlled cultivation provide bioactive compounds that meet clinical application requirements (Elkhateeb et al. 2020). Standardization of bioactive compounds during this method is essential for clinical use because it enables the production of highly pure and potent products (Patel and Goyal 2012). The transition from traditional harvesting to industrial production creates ethical issues because it involves the commercialization of indigenous knowledge while excluding fair compensation for local communities (Kidd 2000). Fair compensation combined with ethical sourcing agreements serve to stop exploitation from occurring.

8.11 Sustainable Practices

The cultivation of mushrooms proves environmentally beneficial because it uses agricultural waste materials as substrates, which reduces pollution while maximizing resource efficiency (Xu et al. 2012). Proper ethical harvesting techniques together with conservation initiatives serve as essential components for protecting ecosystem stability while making medicinal mushroom species available for future use (Wasser 2014).

8.12 Potential Environmental Concerns

Mushroom farming becomes unsustainable if intensive methods are not combined with sustainable practices, which could otherwise result in soil destruction and pollution (Friedman 2016). The practice of using chemical fertilizers and pesticides in commercial mushroom cultivation creates contamination in both soil and water, which endangers the surrounding ecosystems (Valverde et al. 2015). Organic farming practices together with adherence to strict environmental regulations serve as vital measures to reduce these negative impacts (Elkhateeb et al. 2020). Natural sourcing versus biopharmaceutical manufacturing of medicinal mushrooms raises ethical and practical issues for both practices.

8.13 Limitations and Further Considerations

The potential medical uses of medicinal mushrooms face multiple obstacles, which prevent their acceptance in contemporary clinical practice.

8.13.1 The Need for Large-Scale Clinical Investigations

The health benefits of medicinal mushrooms have been shown in preclinical studies, yet there is a scarcity of large-scale randomized controlled trials (Roupas et al. 2012). Establishing precise dosages and safety profiles and measuring efficacy stands as essential for incorporating medicinal mushrooms into evidence-based clinical guidelines (Patel and Goyal 2012). Mainstream medical use of medicinal mushrooms faces uncertainty from regulatory agencies because of insufficient clinical validation (Kidd 2000).

8.13.2 Regulatory Challenges

The implementation of medicinal mushrooms in conventional medicine encounters multiple regulatory obstacles (Wasser 2014). Well-defined legal frameworks are needed to guarantee product quality and patient safety because the differences

between cultivation methods and extraction techniques and bioactive compound concentrations create inconsistencies (Elkhateeb et al. 2020). The absence of standardized manufacturing and labeling practices creates difficulties for healthcare providers as well as consumers in their decision-making processes (Friedman 2016).

8.13.3 Side Effects and Drug Interactions

Bioactive compounds within medicinal mushrooms may cause adverse reactions when taken with prescribed drugs, which can result in drug interactions and contraindications (Sullivan et al. 2006). Polysaccharide compounds in *G. lucidum* mushrooms possess immunomodulatory effects that might conflict with immunosuppressive pharmaceuticals (Lindequist 2013). Healthcare providers need to understand the possible drug interactions when they prescribe medicinal mushrooms to patients (Xu et al. 2012).

8.14 Conclusions

Although medicinal mushrooms have great therapeutic value, ethical sourcing, environmental sustainability, and robust clinical validation, along with regulatory oversight need to be ensured in order to use them responsibly in the healthcare system (Wasser 2014). With the implementation of sustainable harvesting, equitable benefit sharing, and conducting rigorous clinical trials by the scientific and medical communities, the benefits of medicinal mushrooms can be utilized while the risks are minimized (Patel and Goyal 2012). The medicinal mushrooms can be used as therapeutics for the treatment of Alzheimer's disease through NGF stimulation, stress reduction, neurotransmitter modulation, and antioxidant and anti-inflammatory activity. Though the results are encouraging, more large-scale clinical trials are required to confirm these benefits and to assess the safety of their consumption, regulatory issues, and drug interactions. These natural compounds could be used alongside conventional AD treatments to provide a multifaceted approach to treating this multifactorial disease.

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Therapeutic Potential of the Medicinal Mushroom in Parkinson's Disease

9

Sepehr Khosravi, Helia Alizadeh, and Anahita Tarki

Abstract

Parkinson's disease is a progressive neurodegenerative disorder that causes both motor and non-motor symptoms. Although treatments like levodopa help manage symptoms, no therapy currently exists to slow or stop disease progression. Recently, medicinal mushrooms have gained attention as potential neuroprotective agents due to their antioxidant and anti-inflammatory effects. Their complex chemistry and wide range of biological activities make them promising broad-spectrum therapeutics. Species such as *Sarcodon*, *Cyathus*, *Hericium*, *Antrodia*, *Ganoderma*, and *Pleurotus* have been used in traditional medicine. They are now being studied for their potential to treat neurodegenerative diseases, including Parkinson's disease.

Key species like *Ganoderma lucidum*, *Hericium erinaceus*, and *Agaricus blazei* show promise in reducing oxidative stress by lowering reactive oxygen species and activating cellular defense pathways, protecting mitochondrial function, and suppressing neuroinflammation by modulating immune responses. They also influence antiapoptotic signaling and support dopaminergic neurotransmission, which is crucial for Parkinson's disease management. Separately, psychedelic mushrooms containing psilocybin have drawn attention for their

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potential to enhance neuroplasticity and modulate neural networks, which might contribute to long-term therapeutic benefits in neurodegenerative conditions.

This chapter explores the possible neuroprotective mechanisms of medicinal mushrooms in Parkinson's disease, highlighting emerging research and the need for further investigation.

Keywords

Parkinson's disease · Medicinal mushrooms · Mycotherapy · Neuroprotection

9.1 Introduction

Parkinson's disease (PD) is a multisystem disorder consisting of motor and non-motor symptoms. The motor symptoms of this disease are marked by delayed initiation and a gradual decline in the speed and size of repetitive movements (known as motor decrement), along with muscle rigidity and a characteristic slow, coarse resting tremor resembling pill-rolling. Non-motor symptoms may include a reduced sense of smell, RBD (REM sleep behavior disorder), autonomic dysfunction, and other manifestations. This progressive neurodegenerative disorder is characterized by neuronal degeneration with α-synuclein (Lewy bodies) in certain areas, including dopaminergic brain-stem neurons (Lees 2010). PD occurs more frequently as people age, affecting men nearly twice as much as women. Reported incidence ranges from 47 to 77 cases per 100,000 people over 45 years old, and increases to 108 to 212 cases per 100,000 individuals over 65. When adjusted for age and sex, the mortality rate for PD is estimated to be around 60%, exceeding that of the general population. Moreover, the financial impact of Parkinson's disease in the United States is projected to increase from $52 billion in 2017 to $79 billion by 2037. PD is thought to result from multiple causes, involving both genetic and nongenetic factors. About 20% of people with PD have genetic variants with significant effects, known as monogenic PD (Tanner and Ostrem 2024).

The history of PD is closely intertwined with the development of treatments, evolving from chance discoveries to rigorous clinical trials of targeted therapies. Although symptoms resembling Parkinson's were noted in ancient writings, James Parkinson gave the first detailed medical account in 1817. In the mid-nineteenth century, Jean-Martin Charcot significantly clarified and broadened the initial understanding of Parkinson's disease and helped spread knowledge about it internationally. Charcot and his students outlined the clinical range of the disease, distinguishing two primary types: the tremor-dominant form and the rigid/akinetic form. Charcot is credited with being the first to use the term "Parkinson's disease."

In his first medical description of the disease in 1817, James Parkinson expressed hope for the discovery of a remedy that could halt the progression of the disease. Leopold Ordenstein, an intern under Charcot, authored his medical thesis on using belladonna alkaloids to manage Parkinsonian tremors, representing the earliest recognized treatment for PD. These medications act as central anticholinergics and

were later discovered to affect the striatum's balance between cholinergic and dopaminergic systems, leading to improvements in Parkinsonian symptoms. Over the years, the discovery of dopamine deficiency in PD and the understanding of dopamine's synthetic pathway paved the way for the first human trials of levodopa. Levodopa marked a significant milestone in the symptomatic treatment, dramatically improving patients' quality of life. Although there have been breakthroughs in understanding and managing PD, no disease-modifying treatment has been approved to date, and levodopa continues to be the cornerstone of Parkinson's therapy today (Goetz 2011). Recently, medicinal mushrooms have gained attention for their potential neuroprotective effects in PD, mainly through antioxidant, anti-inflammatory, and neurotrophic compounds. However, unclear mechanisms and limited evidence highlight the need for further research. This chapter aims to explore the potential neuroprotective mechanisms of medicinal mushrooms in the context of Parkinson's disease, highlighting both the emerging findings and the need for further research.

9.2 Current Therapeutic Strategies in Parkinson's Disease

Current pharmacologic strategies focus primarily on symptomatic relief, as no treatment has been proven to slow or halt disease progression despite decades of research. Many drugs appeared promising as disease-modifying treatments, but later studies showed their effects were only symptomatic, for example, monoamine oxidase B (MAO-B) inhibitors (Olanow et al. 2009). Levodopa remains the mainstay for managing motor symptoms like bradykinesia, rigidity, and tremor. Other commonly prescribed dopaminergic therapies include dopamine agonists and MAO-B inhibitors. Complications like motor fluctuations and dyskinesias are significant limitations of these therapies. Multidisciplinary care involving physiotherapy, occupational therapy, speech therapy, and psychosocial support is essential to optimize function and quality of life.

Engaging in consistent physical activity, maintaining a nutritious diet, ensuring adequate restful sleep, and minimizing exposure to harmful factors are all associated with reduced mortality rates in PD. These lifestyle measures are essential for supporting patients at any condition stage (Zhang et al. 2022). Levodopa oral formulations are the primary option for managing motor symptoms, but in some instances, tremors might respond less effectively compared to slowness of movement and stiffness. If a patient shows little to no improvement with levodopa, the initial diagnosis may be reconsidered. The period during which a dose of levodopa effectively controls symptoms is called "on" time and usually lasts several hours. This "on" time is interrupted by "off" time, when the medication's benefits wear off and symptoms return. As the disease progresses, the "on" time duration begins to shorten. These motor fluctuations are likely caused by levodopa's short half-life, variable absorption in the gastrointestinal tract, and the ongoing loss of dopaminergic neurons. Strategies often include increasing the total dose, administering

levodopa more frequently, or adding or switching to extended-release formulations to manage these fluctuations.

Frequent adverse effects include involuntary excessive movements (dyskinesia), the development or worsening of hallucinations or behavioral changes, low blood pressure upon standing (orthostatic hypotension), and nausea. Dopamine agonists, used alone or with levodopa, help reduce motor symptoms and fluctuations due to their longer half-life, but are now less commonly used because of their side effects. Nondopaminergic drugs like amantadine and istradefylline can sometimes help reduce motor fluctuations and dyskinesia when added to treatment. Anticholinergic drugs for tremor are now used less often because they can worsen cognition, especially in the elderly. For managing severe or frequent off episodes, on-demand dopaminergic therapies such as subcutaneous or sublingual apomorphine and inhaled levodopa are used. In advanced PD, continuous administration of levodopa through an intrajejunal pump, as well as subcutaneous infusions of apomorphine or levodopa, has been employed. No single approach works for every patient; treatment should be tailored to each individual (Tanner and Ostrem 2024). Nonmotor symptoms have a significant impact on PD, yet there are few evidence-based treatments available. As a result, off-label medications are commonly used. Many of these symptoms tend to worsen as the disease progresses or in response to dopaminergic therapy (Seppi et al. 2019).

9.3 Potential Neuroprotective Mechanisms of Medicinal Mushrooms in Parkinson's Disease

In recent years, medicinal mushrooms have attracted growing interest for their potential neuroprotective effects, mainly due to their bioactive compounds with antioxidant, anti-inflammatory, and neurotrophic effects. However, while preclinical studies and limited clinical observations suggest promising outcomes, the precise mechanisms through which these fungi exert neuroprotective effects remain incompletely understood. Most of the evidence is preliminary, and firm conclusions have not been made. Thanks to their complex chemistry and wide range of biological activities, mushrooms have potential as broad-spectrum therapeutics. Certain medicinal mushrooms, such as *Sarcodon, Cyathus, Hericium, Antrodia, Ganoderma,* and *Pleurotus*, have long been used in traditional medicine and are now actively studied for their potential in treating neurodegenerative diseases. Medicinal mushroom-derived compounds exhibit neuroprotective effects in PD models by targeting multiple cellular pathways. Polysaccharides from *Ganoderma lucidum* (Reishi), extracts from *Hericium erinaceus* (Lion's Mane), and components of *Agaricus blazei* mitigate oxidative stress by reducing reactive oxygen species (ROS) production and enhancing the Nrf2/HO-1 signaling pathway. The formation of ROS is one of the proposed mechanisms of neurodegenerative diseases, often resulting from impaired metabolism and oxidative stress, which contribute to disease progression (Obodai et al. 2014). In experimental models exposed to MPP+ or rotenone, these compounds preserve mitochondrial integrity by stabilizing membrane potential and

supporting complex I activity. Additionally, they suppress neuroinflammation by inhibiting microglial activation, modulating NF-κB signaling, and decreasing pro-inflammatory mediators. Secondary mechanisms include regulation of apoptosis and enhancement of dopaminergic neurotransmission (Cordaro et al. 2022).

9.3.1 Primary Neuroprotective Mechanisms

9.3.1.1 Regulation of Oxidative Stress

Research has demonstrated the antioxidant properties of medicinal mushrooms in PD models:

- *Ganoderma lucidum* polysaccharides: These reduce ROS levels and enhance antioxidant defenses in primary dopaminergic neuronal cultures (Guo et al. 2016).
- *Agaricus blazei* extracts: These attenuate ROS accumulation in SH-SY5Y cell lines (Venkatesh Gobi et al. 2018).
- *Hericium erinaceus* mycelium: This exhibits antioxidant effects in both in vitro and in vivo models. Cordaro et al. (2022) reported that *Hericium erinaceus* and *Coriolus versicolor* activate the Nrf2/HO-1 pathway, bolstering cellular antioxidant responses.

9.3.1.2 Protection of Mitochondrial Function

Medicinal mushrooms have shown protective effects on mitochondrial function:

- *Ganoderma lucidum* extracts: These maintain mitochondrial membrane potential and mitigate MPP+-induced mitochondrial dysfunction in cellular and animal models (Ren et al. 2019).
- *Agaricus blazei* extracts: These counteract rotenone-induced mitochondrial damage in SH-SY5Y cells (Venkatesh Gobi et al. 2018).

9.3.1.3 Anti-Inflammatory Effects

Medicinal mushrooms demonstrate significant anti-inflammatory properties:

- *Ganoderma lucidum*: This inhibits microglial activation and reduces production of pro-inflammatory mediators, including nitric oxide, TNF-α, and IL-1β, in microglial cultures and co-cultures with dopaminergic neurons (Zhang et al. 2011).
- *Antrodia camphorata* extracts: These alleviate neuroinflammation in MPTP-induced mouse models of PD (Lanza et al. 2023).
- *Hericium erinaceus and Coriolus versicolor*: These modulate neuroinflammation by regulating the NF-κB signaling pathway (Cordaro et al. 2022).

9.3.2 Secondary Protective Pathways

9.3.2.1 Antiapoptotic Signaling

Medicinal mushrooms exert antiapoptotic effects, contributing to neuroprotection:

- *Agaricus blazei* extracts: These modulate apoptotic pathways in mouse models of PD by preventing downregulation of antiapoptotic Bcl-2 and inhibiting upregulation of pro-apoptotic Bax and caspases (Gobi et al. 2019).
- *Ganoderma lucidum* extracts: These suppress cytochrome C release and caspase-3 and caspase-9 activation in both cellular and animal models (Ren et al. 2019).

9.3.2.2 Modulation of Neurotransmitter Systems

Medicinal mushrooms also support dopaminergic neurotransmission:

- *Agaricus blazei* extracts: These maintain expression levels of DAT and VMAT2 in mouse models of PD (Gobi et al. 2019).
- *Hericium erinaceus* mycelium: This protects dopaminergic neurons, elevates dopamine levels, and increases the number of tyrosine hydroxylase-positive neurons in MPTP-induced mouse models (Yang et al. 2020).

9.4 Psilocybin's Therapeutic Potential in Parkinson's Disease

While the majority of medicinal mushrooms explored for PD focus on their neuroprotective properties, a distinct group of fungi, psychedelic mushrooms, has recently drawn scientific interest for their effects on mood, cognition, and neuroplasticity.

Psilocybin, a tryptamine alkaloid, is a naturally occurring compound in certain mushroom-forming fungi, notably those within the *Psilocybe* genus, known for their potent psychoactive properties (Studerus et al. 2011). Structurally, psilocybin and related indole alkylamine hallucinogens resemble endogenous compounds such as serotonin, melatonin, and the hypothesized endogenous psychedelic N,N-dimethyltryptamine, all derived from the tryptamine backbone (Gattuso et al. 2023; Nichols et al. 2017; Tylš et al. 2014). Psilocybin is converted by the body into psilocin, the active molecule responsible for the psychedelic effects; psilocin functions as a partial agonist at 5-HT1A receptors. Psychedelics frequently elicit profound and transcendent experiences, which have been linked to heightened brain entropy. In neuroscience, entropy refers to a system's degree of unpredictability and disorder, correlating with increased flexibility and a broader repertoire of dynamic brain states. This enhanced neural adaptability may facilitate novel patterns of brain activity (Carhart-Harris 2018). A comprehensive review by Aleksandrova and Phillips highlights that classical psychedelics, such as psilocybin, promote significant neuronal changes, including structural and functional plasticity, primarily through neurotrophic signaling pathways. These neuroplastic effects are likely driven by

brain-derived neurotrophic factor (BDNF) and the mammalian target of rapamycin (mTOR), which support neuronal growth and connectivity (Aleksandrova and Phillips 2021).

Additionally, research indicates that psychedelics can influence gene expression and immunomodulatory processes (Martin and Nichols 2018). These mechanisms may contribute to the reorganization of dysfunctional cortical networks, potentially by mitigating neuronal inflammation, a process increasingly implicated in addiction, depression, and neurodegenerative disorders such as PD (Nichols et al. 2017). Such findings suggest that psychedelics could foster long-term therapeutic benefits by rewiring pathological neural circuits. However, distinguishing the relative contributions of cellular-level neuroplastic changes versus network-level alterations, such as modulation of the default mode network (DMN), remains a complex challenge. The interplay between these levels of action and their combined impact on therapeutic outcomes warrants further investigation (Halman et al. 2025).

9.5 Future Directions for Psychedelic and Mushroom-Based Therapies

9.5.1 Clinical Trials

Randomized controlled trials (RCTs) are critical to evaluate the safety and efficacy of these compounds in human populations. For instance, a preliminary clinical trial in 2025 demonstrated that psilocybin improved mood, cognitive function, and motor symptoms in PD patients without significant adverse effects (Bradley et al. 2025). This study involved 12 participants (7 males, 5 females) receiving 10 mg and 25 mg doses of psilocybin 2 weeks apart, with outcomes assessed at 7- and 30-day posttreatment. Additionally, a clinical trial investigating *Hericium erinaceus* for non-motor symptoms of PD (ClinicalTrials.gov NCT04428983) was completed in 2023, though results are pending publication. Larger RCTs are needed to confirm these findings, particularly to address unmet needs such as disease-modifying therapies and management of non-motor symptoms like depression and cognitive impairment.

9.5.2 Animal Model Studies

Continued research using diverse animal models, such as rodents and zebrafish, is vital for elucidating mechanisms of action and optimizing therapeutic protocols. Zebrafish models have been employed to study hallucinogenic compounds' physiological and behavioral effects, providing insights into their therapeutic potential and safety profiles (Kyzar and Kalueff 2016). Rodent models, such as those induced by MPTP or rotenone, have demonstrated that medicinal mushrooms like *Ganoderma lucidum* and *Hericium erinaceus* reduce oxidative stress, preserve mitochondrial function, and mitigate neuroinflammation in PD models. These

Table 9.1 Summary of research approaches for mushroom-based Parkinson's disease therapies

Approach	Objective	Existing examples	Future needs
Clinical trials	Assess safety and efficacy in humans	Psilocybin trial (2025), *Hericium erinaceus* trial (NCT04428983)	Larger RCTs targeting motor and non-motor symptoms
Animal models	Investigate mechanisms and optimize treatments	Zebrafish and rodent models for psilocybin and medicinal mushrooms	Broader studies on dosing and administration routes
Neuroimaging and biomarkers	Understand brain changes and detect the disease at much earlier stages	fMRI and PET for connectivity and neurotransmitter systems Alpha-synuclein seed amplification assay to identify prodromal stages of synucleinopathy	Wider use in clinical trials to validate mechanisms and earlier initiation of neuroprotective agents

studies form a foundation for translating preclinical findings into clinical applications, refining dosing regimens, and identifying optimal administration routes.

9.5.3 Neuroimaging and Biomarkers

Advanced neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), are crucial in studying how these compounds affect brain structure and function in PD. fMRI can map alterations in brain connectivity, particularly in regions like DMN, basal ganglia, and raphe nuclei, which are implicated in Parkinson's pathology and psychedelic effects. For example, psilocybin's modulation of serotonin receptors and its influence on brain entropy could be correlated with improvements in motor and non-motor symptoms. PET imaging can quantify changes in dopaminergic and serotonergic receptor density or neuroinflammation markers, offering a deeper understanding of therapeutic mechanisms. Developing new biomarkers for Parkinson's disease enhances the ability to identify the condition at much earlier stages—well before the appearance of clinical motor symptoms. Intervening at this pre-symptomatic or biomarker-only stage may improve the chances of achieving neuroprotection and could lead to more reliable outcomes in drug trials. Incorporating these biomarkers into trial design can enhance efficiency, enable better participant selection, and ultimately accelerate the development and evaluation of disease-modifying therapies (Zarkali et al. 2024) (Table 9.1).

9.6 Conclusion

Integrating clinical trials, animal model studies, and neuroimaging is crucial for developing evidence-based PD therapies using medicinal mushrooms. These approaches will clarify the compounds' effects on neural plasticity, inflammation,

and neurotransmission, addressing critical gaps in current treatments, such as the lack of disease-modifying therapies and inadequate management of non-motor symptoms. Collaborative efforts will be essential to translate these findings into safe and effective clinical interventions.

In 1817, James Parkinson expressed a hopeful vision for the future—that a remedy might one day be found to halt the progression of the disease. More than two centuries later, we are still pursuing that goal. While it is too early to say with certainty whether medicinal mushrooms may represent a step toward fulfilling that hope, preliminary findings have sparked scientific interest. Ongoing and more rigorous research will be essential in determining their true therapeutic potential. Until then, we must wait with cautious optimism to see what future discoveries may reveal.

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Medicinal Mushrooms as an Effective Early Nutritional Intervention for Dementia Management

10

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Abstract

With no cure for dementia, it is becoming a bigger global health issue, which means early and safe interventions are needed. This chapter points out that medicinal mushrooms such as *Hericium erinaceus*, *Ganoderma lucidum*, and *Cordyceps sinensis* can be beneficial as additional nutritional treatments for dementia prevention. These fungi protect the brain by addressing problems such as oxidative stress, brain inflammation, malfunctioning mitochondria, and issues in the connection between gut and brain. *H. erinaceus* has proven to encourage nerve growth factor synthesis and help with mild cognitive impairment (MCI), and *G. lucidum* and *C. sinensis* have shown signs of being anti-inflammatory, antioxidant, and neuroregenerative. This chapter brings together studies from preclinical and emerging human studies to illustrate the potential of these fungi as simple, low-risk agents for the development of integrative therapeutic strategies. Their immunomodulatory and neurotrophic profile makes them especially useful in holistic dementia care. Integrating traditional mycotherapy with neuropharmacology could help medicinal mushrooms introduce a preventive approach to neurology. This chapter supports using these drugs in multidisciplinary ways and calls for structured clinical trials to test their effects in treating neurodegenerative conditions.

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Keywords

Dementia · Medicinal mushrooms · Neuroprotection · Gut · brain axis · Integrative therapy

10.1 Introduction

Dementia is a major public health concern of the twenty-first century. Apart from its socioeconomic ramifications, it also has devastating impact on one's cognitive function and quality of life. In 2019, according to Nichols et al. (2022), we saw over 57.4 million cases of dementia worldwide and by the year 2050 that number is expected to grow to about 152.8 million. This growth is mostly a result of demographic change and population aging, which in turn sees health care systems in low- and middle-income countries unprepared to deal with the growing need. The economic effect is similarly astounding, where we see large burden in direct medical costs, long-term care costs, and the value of informal care that are placed on individuals, families, and national health systems (Nichols et al. 2022). These issues bring to the fore the acute need for early intervention, which in turn may reduce functional decline and economic impact and also at the same time delay progression of the disease. Research indicates that timely diagnosis, risk factor modification, and cognitive preservation do in fact greatly change the course of the disease and also improvement in patient outcomes as well as reduced demand for long-term care (Nichols et al. 2022).

Nutrition is a fundamental determinant of brain health and is one of the most modifiable risk factors linked to the etiology and progression of dementia. An increasing amount of research emphasizes how important dietary patterns are in causing neurodegeneration (Brockdorf and Morley 2021). Diets lacking in important micronutrients, such as antioxidants, omega-3 fatty acids, vitamin B12, and vitamin D, have been repeatedly linked with greater cognitive decline and an elevated risk of dementia (Brockdorf and Morley 2021). It has also been demonstrated that pro-inflammatory diets increase the production of cytokines, which in turn promotes hippocampus atrophy and synaptic dysfunction. Another new mechanism that connects gut health with cognitive integrity is the gut–brain axis. Unbalances in gut microbiota, which are caused by inadequate consumption of fiber and polyphenols, can increase gut permeability, cause systemic inflammation, and eventually impair brain function. A number of dietary therapies such as the Mediterranean diet, ketogenic regimens, and micronutrient supplements have shown promise in delaying cognitive decline and improving brain resilience in response to these discoveries (Brockdorf and Morley 2021).

The therapeutic potential of medicinal mushrooms has garnered renewed attention concurrent with developments in nutritional neuroscience. This field has its roots in traditional medicine but is currently being bolstered by modern biomedical research. Many societies in Asia and Eastern Europe valued mushrooms for their medicinal qualities even before pharmacological neurotherapeutics were developed.

Species such as *Cordyceps sinensis*, *Lentinula edodes* (Shiitake), and *Ganoderma lucidum* (Reishi) were utilized in Traditional Chinese Medicine to promote mental clarity, vigor, and immunological regulation. The use of fungi like *Fomes fomentarius* and *Piptoporus betulinus* for wound healing and antibacterial reasons has also been reported in ethnomycological practices in Eastern Europe, especially in Poland (Kotowski 2019). These customs serve as a basis for current scientific research in addition to reflecting ingrained cultural knowledge.

These ancient claims have currently been validated by modern neuropharmacology, which deals with chemicals produced from mushrooms such as polysaccharides, hericenones, erinacines, triterpenes, and phenolics for their antioxidant and anti-inflammatory and neuroprotective properties. Remarkably, *Hericium erinaceus* has attracted attention because of its ability to enhance production of NGF, which contributes to synaptic plasticity and neurogenesis (Yadav et al. 2020). Similarly, in Alzheimer's as well as Parkinson's diseases, the triterpenes from *G. lucidum* have indicated appealing outcomes in terms of regulating the mitochondrial behavior and for reducing neuroinflammations (Yadav et al. 2020). The investigation of the mushrooms that contain psilocybin, the use of which for a long time was linked to shamanic and spiritual traditions, for the ability to modulate serotonin, primarily through the 5-HT2A receptor, is a very recent development in this area. These relationships are associated with better cognitive flexibility, affective processing, and neuroplasticity (Van Court et al. 2022). These qualities that may be used therapeutically to treat age-related neurocognitive disorders. The medicinal mushrooms are excellent candidates for comprehensive cognitive health programs on account of their natural origin and low toxicity profiles and synergy potential with pharmaceutical and dietary treatments.

10.2 Pathophysiology of Dementia and the Therapeutic Potential of Medicinal Mushrooms

The pathophysiology of dementia is multidimensional, and it includes converging mechanisms like the oxidative stress, mitochondrial dysfunction, chronic neuroinflammation, and even disruption in the gut–brain axis. For instance, Alzheimer's disease is the most common dementia, whereby the accumulation of amyloid-β peptides lead to excessive production of reactive oxygen species and mitochondrial damage in neurons, which activates apoptotic cell death (Lian et al. 2024). At the same time, there is chronic activation of macrophages in the brain, known as microglia, which release pro-inflammatory mediators that worsen neuronal injury (Heneka et al. 2015). Recent indications also associate gut dysbiosis (an imbalance of gut microbiota) with neurodegeneration because microbial variations can trigger systemic and central inflammation and metabolic disruptions on the brain (Cryan et al. 2019). Considering this complex pathology, the increased interest in multitarget treatment strategies, involving medicinal mushrooms like *G. lucidum* (Reishi) and *H. erinaceus* (Lion's Mane), which have been used in folk medicine for centuries, is now explored for its neuroprotective properties.

10.2.1 Oxidative Stress and Mitochondrial Dysfunction

One hallmark of dementia pathology is heightened oxidative stress due to an overabundance of reactive oxygen species (ROS). Since neurons need a lot of energy, they are more likely to be damaged by oxidative stress. If ROS accumulates in the cell, it can oxidize lipids, damage proteins, and cause changes in DNA or RNA, which might then lead to apoptosis (Jiang et al. 2016). Oxidative damage influences mitochondria and is also a symptom of their dysfunction. Damaged mitochondria produce less ATP for the brain and allow more ROS to escape, which leads to a cycle of lacking energy and more cellular damage (Swerdlow 2018). Studies have pointed out that Alzheimer's and Parkinson's diseases are linked to early dysfunction of mitochondria, such as lower respiratory enzyme activity and problems with the membrane potential, as well as oxidative damage to the brain (Swerdlow 2018). Because of this, reducing ROS or boosting mitochondrial health is seen as a way to protect the brain in cases of dementia.

Medicinal mushrooms are known to contain antioxidants and mitochondria-protecting substances that can help prevent these processes. *G. lucidum* has polysaccharides and triterpenes that can help get rid of harmful free radicals in the body. In neuronal cell models, *G. lucidum* polysaccharides (GLPS) were found to reduce the damage caused by hydrogen peroxide. The use of GLPS in treatment prevented the death of neurons under oxidative stress by keeping the mitochondrial membrane strong and balancing the levels of pro- and antiapoptotic proteins (Sun et al. 2017). Similarly, compounds from *H. erinaceus* have been shown to protect the mitochondria in the body. Extracts from *H. erinaceus* reduce the amount of ROS inside the cells, maintain the activity of mitochondrial respiratory complexes, and help stabilize neuronal mitochondrial membranes after toxin exposure (Zhang et al. 2016). Enhanced mitochondrial function has also been noticed in studies where *H. erinaceus* was tested in the lab (Zhang et al. 2016). When *H. erinaceus* was given to animals, markers of oxidative damage decreased and their cognitive abilities improved, suggesting it has antioxidative neuroprotective effects (Zhang et al. 2016).

10.2.2 Neuroinflammation and Immune Modulation

Chronic neuroinflammation, where the brain remains in an inflammatory state, is also responsible for causing dementia. Microglia are the key cells responsible for this process in the nervous system. When everything is working as it should, microglia watch over the body and sweep away debris. In dementia, these neurons are sometimes overly active, usually due to protein deposits like amyloid-β or some other problem. When microglia are activated, they release various pro-inflammatory substances, for example, cytokines (such as interleukin-1β, IL-6, and tumor necrosis factor-α), chemokines, ROS, and nitric oxide, to fight off threats (Heneka et al. 2015). While acute activation of microglia is beneficial, continuing activation for a long time is harmful to neurons. An excessive number of cytokines and reactive molecules harm the neurons and synapses and may upset the balance of proteins,

triggering tau protein to become hyperphosphorylated and form aggregates in Alzheimer's (Heneka et al. 2015). Chronic neuroinflammation thus becomes self-perpetuating: When neurons are injured, they let off signals that help microglia become more active. As time goes on, it creates a loop of neuron damage and increased inflammation that speeds up mental decline (Heneka et al. 2015). Many studies on dementia patients have found signs of inflammation in the affected brain regions, which proves that inflammation is a main part of the disease (Swerdlow 2018).

10.2.3 Gut–Brain Axis and Dysbiosis

The gut–brain axis has become recognized as an important contributor to the development of neurodegenerative diseases. Trillions of microbes in the gastrointestinal tract of humans play a role in metabolism, absorption of nutrients, and the immune system (Cryan et al. 2019). More studies are showing that an imbalance in gut microbiota (dysbiosis) can have wide-ranging effects on the brain. The gut and brain talk to each other in different ways, like with nerve signals (vagal signals), through the immune system (via cytokines), and with special hormones that come from bacteria in the gut (microbially influenced neurotransmitters and metabolites) (Cryan et al. 2019). Research suggests that an unbalance of gut bacteria in dementia can cause both neuroinflammation and neurodegeneration. Some harmful bacteria in the gut or the pro-inflammatory products they release (such as lipopolysaccharide) can increase small intestine permeability and enter the bloodstream, which can lead to inflammation in the brain (Angelucci et al. 2019). Dysbiosis may also lead to a decrease in the production of SCFA, a beneficial microbe metabolite that usually helps regulate the immune system and protects the blood–brain barrier (Angelucci et al. 2019). As a result, an imbalance in the microbiome can cause several other problems. Weakened gut barrier, increased inflammation in the body, activated microglia, and even harm to neurons. Changes in the gut microbiome have been found in people with Alzheimer's and Parkinson's, and altering the microbiota seems to affect brain inflammation and behavior (Cryan et al. 2019). For this reason, having a healthy gut is now linked to brain health, and scientists are investigating probiotics, diet changes, and prebiotics as possible ways to support treatment for cognitive decline.

Medicinal mushrooms may help support a healthy connection between the gut and the brain by supporting good bacteria in the gut and helping the body's immune system. Many edible medicinal mushrooms have a lot of fiber that's hard for our bodies to break down, and this fiber is a good food source for the helpful bacteria in our gut. For instance, polysaccharides from *G. lucidum* were found to help good gut bacteria grow in animals, and they also seemed to stop an imbalance in the gut microbes (Chang et al. 2018). Mice fed *G. lucidum* polysaccharides had more good bacteria in their gut, like *Lactobacillus*, and fewer bad bacteria that can cause inflammation, which helped with things like blood sugar and inflammation in the body (Chang et al. 2018). *G. lucidum* has also been found to help improve the gut's barrier and support the immune system in the gut. Experiments in rats showed that

eating a *G. lucidum* fungus extract helped keep the gut lining strong and kept the immune system working properly in the gut (Chang et al. 2018). *H. erinaceus* also changes the gut bacteria in a similar way. In a recent study on aged mice, adding *H. erinaceus* extract to their diet increased the amount of good gut bacteria and lowered the amount of possibly harmful bacteria. This change in gut bacteria made the levels of inflammation in the brain go down and helped people think and remember better (Li et al., 2020).

10.3 Medicinal Mushrooms with Clinical Relevance in Dementia

The neuroprotective qualities of medicinal mushrooms have been recognized, and their potential to help prevent neurodegenerative illnesses like Parkinson's disease (PD) and Alzheimer's disease (AD) has sparked growing scientific interest. Their antioxidative, immunomodulatory, and neuroprotective properties are the main bioactive components responsible for their therapeutic effectiveness. Among these, *C. sinensis*, *G. lucidum* (Reishi), and *H. erinaceus* (Lion's Mane) have shown encouraging advantages in mitochondrial health, neuroimmune regulation, and cognitive function. These characteristics make medicinal mushrooms attractive options for managing and preventing dementia (Araújo-Rodrigues et al. 2024).

10.3.1 *Hericium erinaceus* (Lion's Mane)

A well-known medicinal fungus with significant neuroprotective qualities, *H. erinaceus* is especially pertinent to neurodegenerative conditions like Alzheimer's disease and moderate cognitive impairment (MCI). Hericenones, which are present in the fruiting body, and erinacines, which are concentrated in the mycelium, are the two families of chemicals mainly responsible for its neuroactive potential. Notably, erinacine A, a mycelium-derived diterpenoid, is a viable treatment option for neurodegenerative diseases due to its exceptional capacity to penetrate the blood–brain barrier (Li et al., 2020). The stimulation of Nerve Growth Factor (NGF) synthesis is one of the main ways that *H. erinaceus* carries out its neuroprotective effects. NGF is essential for synaptic plasticity, neuronal growth, and survival, especially in cholinergic neurons of the basal forebrain, which gradually die off in Alzheimer's disease. *H. erinaceus* counteracts cognitive decline, supports synaptic integrity, and encourages neurogenesis by increasing NGF synthesis (Araújo-Rodrigues et al. 2024).

These advantages are supported by clinical and preclinical studies. According to research, erinacine A increases the production of NGF in the cortex and hippocampus, which promotes synaptic plasticity and reduces oxidative stress and neuroinflammation, two main causes of neurodegeneration (Li et al., 2020). Furthermore, in animal models, *H. erinaceus* has shown effectiveness in lowering beta-amyloid plaque deposition, a defining feature of Alzheimer's pathology, indicating possible disease-modifying benefits (Araújo-Rodrigues et al. 2024).

Significant gains in Mini-Mental State Examination (MMSE) scores were observed in a randomized controlled trial (RCT) evaluating *H. erinaceus* supplementation in people with MCI as compared to the placebo group. Additionally, the effectiveness of erinacine A-enriched *H. erinaceus* mycelia (EAHE) in early AD patients was examined in a double-blind, placebo-controlled clinical experiment (Li et al., 2020). Significant cognitive benefits, such as increased scores on the Cognitive Abilities Screening Instrument (CASI) and decreased reliance on instrumental activities of daily living (IADL), were demonstrated by participants who received EAHE (350 mg each capsule, containing 5 mg/g erinacine A) for 49 weeks. In addition, contrast sensitivity improved, which may indicate neuroprotective benefits on visual processing (Li et al. 2020). Because of its capacity to penetrate the blood–brain barrier and its NGF-stimulating qualities, *H. erinaceus* offers a new therapeutic approach for the treatment of dementia.

10.3.2 *Ganoderma lucidum* (Reishi)

Reishi, or *G. lucidum*, has been the subject of much research due to its neuroprotective qualities, especially in relation to neurodegenerative illnesses like AD and PD. According to Lian et al. (2024), triterpenes and polysaccharides, which are bioactive substances with notable anti-inflammatory, antioxidative, and neuroimmune-modulating properties, are primarily responsible for its therapeutic potential. One of the main causes of dementia, chronic neuroinflammation, can be significantly reduced with Reishi. Its triterpenes, such as lucidenic and ganoderic acids, reduce neuronal injury by altering microglial activity and changing their phenotype from pro-inflammatory (M1) to anti-inflammatory (M2). This change is essential because long-term microglial activation aggravates the neurodegenerative processes in Parkinson's and Alzheimer's diseases (Araújo-Rodrigues et al. 2024).

Reishi's antioxidant qualities help in protecting neurons. While polysaccharides increase the activity of natural antioxidant enzymes such as glutathione peroxidase (GPx) and superoxide dismutase (SOD), triterpenes eliminate reactive oxygen species (ROS). This dual effect lessens oxidative stress, preventing damage to neurons (Lian et al. 2024). Additionally, Reishi protects against tau hyperphosphorylation, which is a defining feature of AD pathogenesis. Triterpenes decrease the formation of neurofibrillary tangles and neuronal dysfunction by inhibiting glycogen synthase kinase-3β (GSK-3β), an enzyme essential for tau phosphorylation. Furthermore, Reishi has been shown to protect dopaminergic neurons from oxidative and inflammatory damage in models of Parkinson's disease, which slows the progression of the disease (Araújo-Rodrigues et al. 2024).

In addition to modifying the condition, *G. lucidum* has shown promise in treating mood swings and sleep issues that are linked to dementia. Reishi supplementation has been linked to benefits in anxiety, sadness, and sleep quality, according to clinical trials. According to Lian et al. (2024), these effects are probably mediated via its control of GABAergic and serotonergic neurotransmission, which are important for mood and sleep-wake cycle regulation. Overall, these findings highlight *G. lucidum*'s potential as a neuroprotective and symptomatic treatment for dementia.

10.3.3 *Cordyceps sinensis*

With a lengthy history in traditional medicine, the parasitic fungus *C. sinensis* has drawn interest for its neuroprotective properties, especially in relation to energy metabolism and mitochondrial function. Cordycepin and adenosine derivatives are among the main bioactive substances that improve cellular energy generation and shield neurons from metabolic stress, which is becoming more widely acknowledged as a significant contributing factor to neurodegenerative illnesses (Araújo-Rodrigues et al. 2024).

The capacity of *C. sinensis* to enhance mitochondrial bioenergetics is one of its main neuroprotective mechanisms Research indicates that cordycepin decreases mitochondrial dysfunction, which is a major aspect of AD and PD pathology, stabilizes mitochondrial membranes, and increases the synthesis of adenosine triphosphate (ATP) (Lian et al. 2024). This enhancement in energy metabolism could delay cognitive aging and maintain neural function. Additionally, *Cordyceps* has antioxidant and anti-inflammatory properties. Its bioactive components reduce neuroinflammation by suppressing pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. According to Araújo-Rodrigues et al. (2024), *Cordyceps* also strengthens antioxidant defenses, reducing oxidative stress and maintaining neural integrity.

Furthermore, *C. sinensis* has been connected to improved synaptic plasticity, which is a basic mechanism that underlies memory and learning. In animal models of AD, preclinical research shows that supplementing with *Cordyceps* improves long-term potentiation (LTP), boosts hippocampus synaptic function, and lessens cognitive impairments (Lian et al. 2024).

Increasing experimental and clinical data supports medicinal mushrooms' therapeutic potential in dementia management. *H. erinaceus*, *G. lucidum*, and *C. sinensis* have distinct neuroprotective qualities due to their capacity to regulate neuroinflammation, oxidative stress, mitochondrial function, and synaptic plasticity. As our understanding of their bioactive chemicals grows, these fungi may be used as adjunct medicines in the prevention and management of cognitive decline, supporting the growing convergence of traditional medicine and modern neuroscience.

10.4 Clinical Application: Integrating Medicinal Mushrooms into Dementia Care

With a rising incidence in older populations and few effective treatments to stop or reverse cognitive deterioration, dementia continues to be a significant global health concern. The potential of medicinal mushrooms as a supplemental treatment for neurodegenerative diseases, especially in the early phases of cognitive impairment, is highlighted by recent study. Through their bioactive compounds, which modulate neuroinflammation, promote neurogenesis, and enhance synaptic plasticity, species like *H. erinaceus* (Lion's Mane), *G. lucidum* (Reishi), and *Ophiocordyceps sinensis* (*Cordyceps*) exhibit neuroprotective properties (Spelman et al. 2017). Because

dementia is complex, incorporating medicinal mushrooms into patient care early and specifically may improve cognitive resilience and slow the progression of the condition (Docherty et al. 2023).

10.4.1 Timing of Intervention: Early Versus Late-Stage Dementia

There have been encouraging results from using medicinal mushrooms, especially *H. erinaceus*, in dementia treatment, when started early in the cognitive decline process. According to research, people with mild cognitive impairment (MCI) benefit more cognitively from supplements than people with more severe dementia (Bizjak et al. 2024). The bioactive substances found in *H. erinaceus*, such as erinacines and hericenones, are essential for promoting the synthesis of nerve growth factor (NGF), which promotes synaptic plasticity and neuronal survival. Early intervention enables optimal neuroprotective effects, potentially improving memory, executive function, and general cognitive resilience (Bizjak et al. 2024). Additional evidence for these conclusions comes from a systematic review that examined in vivo research on dietary mushroom supplementation for cognitive impairment. Twenty-two out of twenty-five animal studies that looked at the effects of *H. erinaceus* (Lion's Mane), *G. lucidum* (Reishi), and *O. sinensis* (*Cordyceps*) on cognitive function showed notable cognitive advantages (Nkodo 2019). Interestingly, statistically significant improvements in cognitive tests were also observed in two out of three human randomized controlled trials (RCTs) (Nkodo 2019). These results support the possibility that medicinal mushrooms could be used as a successful early intervention in neurodegenerative disorders. These results emphasize the potential for better patient outcomes when incorporated at the earliest indications of cognitive deterioration, underscoring the need of promptly implementing medicinal mushrooms as a supplemental therapy in dementia management (Bizjak et al. 2024; Nkodo 2019).

10.4.2 Optimal Dosage and Formulation

The possible neuroprotective and cognitive-enhancing qualities of medicinal mushrooms have drawn more and more attention. In their double-blind, placebo-controlled study, Docherty et al. (2023) examined the short-term and long-term impacts of *H. erinaceus* supplementation on young adults' mood and cognitive function. They found that over the course of a 28-day intervention period, there was a trend toward decreased subjective stress and an improvement in cognitive processing speed. To validate these benefits, more research with bigger cohorts is required, as the study was constrained by a small sample size.

In addition to *H. erinaceus*, other medicinal mushrooms may potentially have positive effects on mood and cognition. According to Spelman et al. (2017), *G. lucidum* has adaptogenic qualities that could lessen cognitive damage brought on by stress. Likewise, *Cordyceps* sinensis has been linked to enhanced

neuroprotection and mitochondrial activity, which may improve focus and mental clarity (Spelman et al. 2017). These fungi's combined effects on neuroplasticity and neuroinflammation imply that medicinal mushrooms could be used in conjunction with other strategies to preserve cognitive health, especially in groups that are susceptible to neurodegeneration and occupational stress.

The main reason Lion's Mane is of medicinal worth is the presence of beta-glucan polysaccharides, hericenones, and erinacines in the mushroom (Spelman et al. 2017). Finding the right dose and formulation matters most when trying to address neurological problems or cognitive decline. Both standardized extracts and whole mushrooms have different active substances, rates of absorption, and effectiveness. Higher concentrations of erinacines (found in the mycelium) and hericenones (produced from the fruiting body) are present in standardized extracts; these compounds have been demonstrated to increase NGF expression and foster neurogenesis (Spelman et al. 2017). Whole mushrooms typically have lesser amounts of these neuroactive substances, despite being rich in a wider variety of polysaccharides and antioxidants. As a result, although whole mushrooms could be beneficial for general health, a larger intake is frequently needed to have the same neurological effects as standardized extracts (Spelman et al. 2017). Preclinical and clinical research have yielded beneficial therapeutic ranges for the ideal dosage of Lion's Mane. Standardized extract doses ranging from 500 mg to 3000 mg daily have been used in human research; greater doses have been shown to provide more noticeable cognitive advantages, especially in people with mild cognitive impairment (Spelman et al. 2017). The compound's wide safety margin is highlighted by animal studies that show neuroprotective benefits at dosages as high as 5000 mg/kg (Spelman et al. 2017). Higher doses might be more beneficial for therapeutic purposes, according to these findings, but additional research is required to fine-tune the best dosing techniques.

The effectiveness of Lion's Mane varies with its various formulations. Tablets and capsules, which usually include standardized extracts, are taken once or twice a day and contain 500–1500 mg per serving. Higher dosages, typically 3–5 grams daily, are needed to get comparable results with powdered whole mushroom formulations (Spelman et al. 2017). Depending on strength, tinctures and liquid extracts, especially those that use alcohol-based extraction, offer quick absorption; dosages of 1–3 milliliters per day are advised (Spelman et al. 2017). With few documented side effects, long-term usage of Lion's Mane seems to be well tolerated. According to studies, neurogenesis and NGF regulation necessitate prolonged exposure to bioactive substances, therefore consistent supplementation for at least 8–16 weeks is required to see detectable cognitive improvements (Spelman et al. 2017). Considering its good safety record, Lion's Mane might be a good supplementary treatment for neurodegenerative diseases, but more extensive clinical trials with strict procedures, bigger sample sizes, and longer follow-up times are necessary to confirm its long-term effectiveness.

10.4.3 Safety Considerations and Drug Interactions

In Alzheimer's disease (AD), *G. lucidum* has shown great therapeutic promise, especially in lowering neuroinflammation and preventing cognitive decline. Improved scores on the ADAS-cog, NPI, and WHOQOL-BREF tests demonstrate that the combination of memantine and standardized polysaccharide extracts of *G. lucidum* (SPGL) produces better cognitive and behavioral improvements than memantine alone (Chen et al. 2024). Furthermore, a randomized controlled trial with 123 AD patients found that taking 1800 mg of *G. lucidum* polysaccharide extract orally three times a day for 8 weeks significantly decreased fatigue scores and the severity of Clinical Global Impression (CGI), indicating possible advantages in treating AD-related neurasthenia symptoms (Chen et al. 2024). In addition to its cognitive benefits, *G. lucidum* has strong neuroprotective and anti-inflammatory properties through regulating the NF-κB and MAPK signaling pathways, which inhibits the release of pro-inflammatory cytokines such TNF-α, IL-6, and IL-1β (Chen et al. 2024). It has been discovered that the triterpenoid components of *G. lucidum*, such as methyl ganoderate G1, lingzhine E, and lingzhine F, enhance antioxidant defenses by lowering the production of reactive oxygen species (ROS) and oxidative stress in brain cells (Chen et al. 2024). Ganoderic acid D (GAD) has been shown to increase telomerase activity, possibly contributing to its antiaging effects in neurological diseases (Chen et al. 2024). By preventing NF-κB activation, the chemical Ganoderterpene A has also been shown to repair neuroinflammatory damage and preserve mitochondrial activity in BV2 microglial cells, hence lowering neuroinflammation (Chen et al. 2024). According to these results, supplementing with *G. lucidum* could help improve Alzheimer's through joint actions on underlying causes such as neuroinflammation and high levels of oxidative stress, as well as by helping treat cognitive damage (Chen et al. 2024).

10.5 Conclusion

Medicinal mushrooms may play an important role in early nutritional care for people with dementia by providing accessible and valuable new therapeutic paths. Bioactive substances in these fungi give them the ability to act on various brain processes, such as oxidative stress, brain inflammation, energy in the brain cells, and support in the gut–brain connection. With their well-documented safety and positive clinical results, medicinal mushrooms could be considered a suitable supplement to current dementia therapies, mainly in the earlier stages of cognitive decline. Strong evidence from additional studies and clinical practice will be needed to improve outcomes and make these natural methods a standard part of care for dementia worldwide.

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The Role of Medicinal Mushrooms in Brain Development and Aging

11

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Abstract

The human brain undergoes dynamic changes across the human lifespan, from the critical periods of neurodevelopment in early life to structural and functional decline associated with aging. As scientific interest grows in natural interventions via functional foods that support cognitive health, medicinal mushrooms have emerged as promising superfoods with the potential to promote brain development and delay age-related neurodegeneration. This chapter explores the neurobiological benefits of select medicinal mushrooms and their active compounds across the lifespan. It explores the bioactive properties of key medicinal mushrooms such as *Hericium erinaceus* (Lion's Mane), *Ganoderma lucidu*m (Reishi),

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and *Cordyceps sinensis* and their implications for neurodevelopmental and neuroprotective processes attributed to their rich neuroactive compounds such as hericenones, erinacines, polysaccharides, terpenoids, and antioxidants that have demonstrated the ability to modulate neurogenesis, enhance nerve growth factor (NGF) production, reduce oxidative stress, and regulate inflammatory pathways. During early brain development, these actions may support cognitive maturation, synaptic plasticity, and the formation of robust neural networks for memory formation while in the aging populations they offer protection against cognitive decline, improve mood and sleep, and delay the onset of neurodegenerative diseases such as Alzheimer's and Parkinson's. This chapter reviews evidence from experimental, clinical, and ethnobotanical studies to examine how medicinal mushrooms influence brain structure and function throughout life, ultimately demonstrating medicinal mushrooms as promising natural agents in promoting cognitive vitality from infancy through old age.

Keywords

Medicinal mushrooms · Cognitive health · Neurodevelopment · Neurotrophic · Synaptic plasticity

11.1 Introduction

Brain development, which begins in prenatal and continues into early adulthood, is characterized by rapid changes in both structure and function (Kolb 2020; Gilmore et al. 2018). During the first 2–3 years of life, there is a high rate of neurogenesis, synaptogenesis, and myelination (Lebel and Deoni 2018). This time frame is crucial for behavioral and cognitive development, which affects results in later life (Gilmore et al. 2018). As gene expression and chromatin accessibility in the prefrontal cortex exhibit significant reconfigurations at the prenatal-to-postnatal transition, this development is most rapid during the prenatal period and early childhood, involving significant changes in the size, shape, and organization of the brain (Estrin and Bhavnani 2020). These changes continue into adulthood (Herring et al. 2022). However, as people age, structural and functional changes take place, which raises the risk of memory impairment, increases susceptibility to neurodegenerative disorders, and causes a progressive deterioration in cognitive performance (Lee and Kim 2022). The structure and function of the brain are affected by age, sex, and ethnicity, and its development is impacted by genetic, environmental, and biochemical factors (Sultana et al. 2024).

High oxidative stress, inflammation, and mitochondrial dysfunction, together with decreased neurophysiological functioning and impaired neuroplasticity, are all indicators of brain aging (Zia et al. 2021; Marzola et al. 2023). According to Marzola et al. (2023), these alterations increase the risk of neurodegenerative illnesses and cognitive decline. Progressive neuronal loss and the buildup of toxic protein aggregates are hallmarks of neurodegenerative disorders such as Parkinson's disease

(PD) and Alzheimer's disease (AD) (Lelos 2020; Hulse and Bhaskar 2022). Also, there are no proven cures for these age-related illnesses, which impact millions of people globally (Salahuddin et al. 2021; Liu et al. 2022a. The main neuropathological characteristics of AD are tau tangles and β-amyloid plaques, whereas Lewy bodies that contain α-synuclein characterize PD (Liu et al. 2022b; Hulse and Bhaskar 2022). Since these neurological disorders place a heavy burden on healthcare systems and lower the quality of life for those who are affected, current research focuses on comprehending these mechanisms and creating therapeutic strategies, such as repurposing small-molecule drugs to modulate toxic protein aggregates (Liu et al. 2022a, b).

A potential treatment option for preserving cognitive function and halting neurodegeneration is neuroprotective medication. According to Mohd and Sirajudeen (2020) and Pekdemir et al. (2024), these substances, which include natural products and their bioactive constituents, boost neuronal survival and function through a variety of methods of action. These substances work by modifying the neuroinflammatory reactions, oxidative stress, and protein aggregation linked to neurodegenerative diseases (Pekdemir et al. 2024). Due to their various bioactive compounds and potential cognitive benefits, medicinal mushrooms have become one of the most promising natural neuroprotective agents. These fungi have a wide range of pharmacological activities, such as immunomodulating, anti-inflammatory, and antioxidant qualities (Venturella et al. 2021). Numerous studies have demonstrated the potential advantages of medicinal mushrooms on cognition. According to previous research by Ba et al. (2022), mushrooms' anti-inflammatory, cholinesterase inhibitory, and antioxidant qualities have been linked to their neuroprotective qualities. Although further research is required, several species, such as *Hericium erinaceus* and *Ganoderma lucidum*, have shown neuroprotective potential (Badalyan and Rapior 2021). According to epidemiological research, there was a dose-dependent association between frequent mushroom consumption and improved cognitive function in several categories (Cha et al. 2024a).

Neurodegenerative illnesses including Parkinson's and Alzheimer's are significantly impacted by neuroinflammation (Kwon and Koh 2020). Pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α are released by activated microglia and astrocytes, which are important regulators of inflammatory responses in the central nervous system (Kwon and Koh 2020). The development of neurodegeneration is aided by the elevated oxidative and nitrosative stress caused by this persistent inflammation. Because *G. lucidum's* extract suppresses microglial activation and shields dopaminergic neurons in Parkinson's disease models by modifying cytokine expression and downregulating the iNOS/NLRP3 pathway, thus demonstrating encouraging anti-inflammatory and neuroprotective effects (Ren et al. 2022). By blocking TLR4/MyD88-mediated NF-κB and MAPK signaling pathways, triterpenoids from *G. lucidum*, including *ganodermanontriol* and *ganoderterpene A*, reduce inflammatory reactions (Kou et al. 2021a). Furthermore, via inhibiting the TLR4/NF-κB pathway, additional medicinal mushrooms like as *H. erinaceus, Antrodia camphorata*, and *Cordyceps* spp. have anti-neuroinflammatory properties (Kushairi et al. 2020b).

Medicinal mushrooms' potential as supplemental therapy for brain health across the lifespan is highlighted by the mounting body of studies demonstrating their neuroprotective benefits (Cha et al. 2024b) 2024a, b). As interest in natural and holistic approaches to cognitive health develops, greater study is needed to explain the particular processes by which these mushrooms impact brain development and aging (Venturella et al. 2021; Cha et al. 2024b) 2024a, b). Clinical research exploring their effectiveness, appropriate doses, and long-term effects is necessary to demonstrate their involvement in neuroprotection and cognitive improvement (Badalyan and Rapior 2021). Medicinal mushrooms may prove to be useful friends in the pursuit of good aging and lifetime cognitive resilience as the scientific study continues to reveal their therapeutic potential.

11.2 Brain Development: The Foundations of Cognitive Health

Cognitive health is the development and maintenance of mental abilities that support independence, social connection, and recovery from illness or injury (Puri et al. 2023). Poor nutrition and growth early in life are associated with poorer performance on tests of motor development and cognitive functioning, as well as deficits in social skills, attention, learning, and educational achievement (DiGirolamo et al. 2020). Consuming food rich in biologically active compounds, such as polysaccharides, proteins, peptides, terpenoids, polyphenols, vitamins, and minerals—many of which are found in medicinal mushrooms—supports brain development by promoting neuroprotection, reducing inflammation, and enhancing antioxidant and immunomodulatory functions (Łysakowska et al. 2023).

11.2.1 Key Stages of Brain Development

Neurodevelopment begins with neural tube formation at 28 days postconception, followed by cell proliferation, migration, and maturation. While these processes occur solely in gestation, others, like neurogenesis and myelination, extend into early adulthood. Peak synapse development and brain growth occur between 34 weeks postconception to 2 years of age (Irvine et al. 2022). To support optimal fetal development and offspring cognitive function, it is recommended that pregnant women consume adequate, but not deficient or excessive, sources of nutrients (e.g., vitamin D, folate, choline, and iron), in addition to other food components (e.g., fiber, fat, and proteins) (Irvine et al. 2022).

Brain development occurs in phases, with major transitions shaping early behavior and cognition. By about 3–4 months of age, Around 3 to 4 months of age, the transient cortical structure governing fetal and neonatal behavior is replaced by the cortical plate, enabling a shift from general movements to goal-directed actions like reaching. The hippocampus, essential for facial and scene recognition as well as spatial memory, develops from approximately 32 weeks of gestation until at least

18 months postnatally. The prefrontal cortex, responsible for attention and multitasking, undergoes rapid early development within the first 6 months of life, but its maturation continues into the third decade. Since the brain's foundational structure and capacity is largely established before age 3, inadequate early development can have lasting consequences on education, work potential, and mental health, posing significant societal costs (Cohen Kadosh et al. 2021).

The brain reaches approximately 90% of its adult size by age 6 years, but the gray and white matter subcomponents continue to undergo dynamic changes throughout adolescence. The prefrontal cortex continually reconstructs, consolidates, and matures (Norris et al. 2022).

11.2.2 Role of Neurotrophic Factors in Brain Growth and Synaptic Plasticity

Brain-derived neurotrophic factor (BDNF) supports neural development, synaptic plasticity, neuronal survival, and cognitive functions like memory and learning (Zhang et al. 2024). It does this by activating tropomyosin receptor kinase B (TrkB) (Costa et al. 2022). This activation initiates signaling pathways that promote the development and maturation of neurons, which are essential for proper brain growth. Alterations in BDNF levels have been linked to several neurodegenerative diseases, underscoring its role in maintaining neuronal health and supporting brain development (Azman et al. 2022).

Neuroplasticity is the brain's ability to reorganize neural networks in response to social, learning, and nutritional influences, a process particularly active during adolescence. Structural plasticity involves physical changes in neurons and synapses, enabling adaptation, while functional plasticity enhances neural efficiency and synchrony, impacting cognitive and behavioral processes like attention, memory, and perception. These forms of plasticity continue into adulthood, shaping brain structure and function (Norris et al. 2022; Marzola et al. 2023). In structural plasticity, BDNF regulates actin dynamics within dendritic spines, leading to their growth and stabilization (Keifer 2022), while, in functional plasticity it enhances synaptic transmission by modulating the activity of neurotransmitter receptors, including NMDA and AMPA receptors, leading to increased synaptic strength and efficiency, which are fundamental for cognitive processes like learning and memory formation (Keifer 2022).

11.2.3 Influence of Diet and Natural Compounds on Cognitive Function

A diet rich in antioxidants, anti-inflammatory compounds, and neuroprotective nutrients—such as berries, leafy greens, medicinal mushrooms, nuts, and omega-3 fatty acid-rich fish—along with natural compounds like alkaloids, polyphenols, and terpenoids, plays a significant role in cognitive function. These nutrients exert their

effects through mechanisms such as reducing inflammation, oxidative stress, and promoting memory and neurogenesis (Ruyi et al. 2025; Ngo et al. 2025). Adhering to dietary patterns such as the Mediterranean, plant-based, or low-carbohydrate diets has been linked to slower cognitive decline and a lower risk of neurodegenerative diseases (Ruyi et al. 2025). However, a higher intake of dietary fats and low-carbohydrate diets, such as the Keto diet, may increase levels of low-density lipoprotein (LDL) cholesterol and triglycerides in the blood, potentially harming the cardiovascular and cerebrovascular systems and accelerating cognitive decline (Ruyi et al. 2025).

Overall, incorporating a variety of nutrient-rich foods and natural compounds into one's diet supports cognitive health and may help prevent age-related cognitive decline.

11.3 Medicinal Mushrooms and Neurodevelopment

Medicinal mushrooms have anti-inflammatory and antioxidant properties, but they also support neurogenesis and synaptic plasticity, which are critical for memory, learning, and cognitive resilience (Ba et al. 2022). For synaptic function and neuronal survival, neurotrophic substances, including brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) are essential (Habtemariam 2018). *H. erinaceus* is a potential treatment for neurological disorders like Alzheimer's and Parkinson's diseases because it contains bioactive compounds like β-glucan polysaccharides, hericenones, and erinacine terpenoids (Deshmukh et al. 2021). These compounds have also been shown to promote neurite outgrowth and nerve growth factor (NGF) synthesis (Skube et al. 2022). Studies conducted in vitro on models of axonal damage have shown that it has neuroprotective properties and is more effective than NGF alone (Üstün and Ayhan 2019; Szućko-Kociuba et al. 2023). Furthermore, clinical trials have shown that *H. erinaceus* possesses anti-inflammatory qualities and is well tolerated (Yadav et al. 2020). Current data indicates that *H. erinaceus mycelia* enriched with erinacines may be beneficial for a variety of neurological diseases, while further study is required to properly comprehend its therapeutic potential (Yadav et al. 2020).

11.3.1 Bioactive Compounds in Medicinal Mushrooms Supporting Brain Growth

Modern scientific research has begun to elucidate the bioactive compounds responsible for these effects, providing insights into their potential mechanisms of action. Important bioactive chemicals in mushrooms, including polysaccharides (e.g., beta-glucans), triterpenes, phenolic compounds, and ergothioneine, help to promote brain development and function (Kumar et al. 2021).

H. erinaceus contains various bioactive compounds, including hericenones and other aromatic compounds, which are typically extracted from the fruiting bodies

(Xie et al. 2022; Wang et al. 2024b). Extraction methods often involve organic solvents like methanol or acetone, followed by chromatographic techniques for isolation (Xie et al. 2022; Wang et al. 2024b). These compounds have demonstrated numerous health benefits, such as anticancer, antioxidant, anti-osteoporotic properties, and in treating various conditions, including cognitive disorders, diabetes, and inflammation (Xie et al. 2022). Research has revealed that hericenones can stimulate nerve growth factor synthesis, suggesting possible applications in dementia prevention and treatment (Wang et al. 2024a). Hericenones, low molecular weight substances found in *Hericium* species, have shown potential for neuroregeneration due to their ability to cross the blood–brain barrier (BBB) (Rascher 2020). These compounds, along with erinacines, can stimulate the production of neurotrophins like NGF and BDNF (Rascher 2020; Martínez-Mármol et al. 2023). Neurotrophins play crucial roles in neural survival and regeneration, making them promising therapeutic agents for neurodegenerative diseases and CNS injuries (Xu et al. 2019). Furthermore, *erinacine S* enhances neurite outgrowth and axon regeneration by increasing neurosteroid levels in neurons (Lin et al. 2023). *H. erinaceus* mycelium and *erinacine A* have been shown to improve spatial learning in aging mice fed high-fat, high-sugar diets, while reducing neuroinflammation and metabolic dysfunction (Tsai et al. 2019).

Beta-glucans, polysaccharides found in fungi and other organisms, have gained attention for their diverse biological activities. These compounds, particularly those from mushrooms, exhibit unique structural features like β-1,3-glucans with β-1,6-side chains and triple helix conformations, contributing to their immunomodulatory properties (Mirończuk-Chodakowska et al. 2021). As biological response modifiers, β-glucans can activate immune cells and receptors, enhancing anti-tumor responses and cytokine production (Varnosfaderani et al. 2024). Their potential extends to neurological health, with evidence suggesting that early-life microbiome–immune interactions influence neurodevelopment (Pronovost and Hsiao 2019; Cerletti et al. 2021).

Ergothioneine (ET) is a potent antioxidant with neuroprotective properties that crosses the blood–brain barrier and is taken up by neurons via the OCTN1 transporter (Ishimoto and Kato 2022). ET protects hippocampal neurons against oxidative stress by reducing reactive oxygen species, increasing antioxidant gene expression, and decreasing apoptosis (Kushairi et al. 2020a). In vitro studies show that ET promotes neurogenesis and neuronal maturation (Ishimoto and Kato 2022). ET also prevents neuronal death caused by 6-hydroxydopamine, a neurotoxin used in Parkinson's disease models (Yuzawa et al. 2024). Oral administration of ET has demonstrated antidepressant effects in mice and improved memory function in both mice and humans (Ishimoto and Kato 2022). As ET levels decline with age, dietary supplementation may be beneficial for maintaining brain health and combating neurodegeneration (Paul 2022). These findings suggest that ET plays a crucial role in neuroprotection and cognitive function.

Recent studies have highlighted the neurotrophic potential of triterpenes and other compounds found in medicinal mushrooms. Lanostane triterpenoids isolated from *Laetiporus sulphureus* and *Antrodia* sp. have been shown to enhance nerve

NGF and BDNF expression in human astrocytoma cells (Venturella et al. 2021; Hassan et al. 2022). These neurotrophins play crucial roles in neuronal survival and synaptic plasticity, and their altered levels are associated with neurodegenerative diseases (Azman and Zakaria 2022). *G. lucidum* (Reishi) contains various bioactive compounds, including triterpenoids like *ganoderic* acids, which have demonstrated potential in treating neurological disorders (Ahmad et al. 2021). These findings suggest promising avenues for developing treatments for neurodegenerative diseases.

Cordycepin, a bioactive nucleoside extracted from *Cordyceps* mushrooms, exhibits significant neuroprotective properties (Soltani et al. 2018). In glutamate-induced neurotoxicity models, cordycepin protects hippocampal neurons by reducing reactive oxygen species production, lowering intracellular calcium levels, and activating adenosine A1 receptors (Sun et al. 2024). Studies on rotenone-induced Parkinson's disease (PD) rat models demonstrate that cordycepin improves motor function, increases dopaminergic neurons, and maintains dopamine levels by suppressing apoptosis through mitochondrial pathway regulation (Jiang et al. 2019). Furthermore, in lipopolysaccharide-induced PD models, cordycepin exhibits neuroprotective effects by inhibiting TLR4/NF-κB/NLRP3-mediated pyroptosis, a form of programmed cell death associated with inflammation (Sun et al. 2020). In MPTP-induced PD mice, cordycepin mitigated behavioral disorders, reduced neuroapoptosis, and inhibited microglial activation by suppressing PI3K/AKT/mTOR and MAPK signaling pathways (Wang et al. 2024a). These findings collectively highlight cordycepin's potential as a neuroprotective agent, suggesting its possible development as a natural medicine or healthcare supplement for treating neurodegenerative disorders like Parkinson's disease.

Cordycepin demonstrates neuroprotective effects against various forms of neuronal injury from glutamate-induced toxicity by reducing reactive oxygen species (ROS) production, lowering calcium levels, and inhibiting acetylcholinesterase (AChE) activation (Sun et al. 2024). In Alzheimer's disease models, cordycepin attenuates β-amyloid and ibotenic acid-induced neuronal hyperactivity and excessive membrane depolarization (Yao et al. 2019). Electrophysiological studies reveal that cordycepin suppresses both glutamatergic and GABAergic synaptic transmission in hippocampal CA1 pyramidal neurons (Wang et al. 2022). Notably, these neuroprotective effects are primarily mediated through the activation of adenosine A1 receptors, as demonstrated by the reversal of cordycepin's effects using A1 receptor antagonists (Yao et al. 2019; Cao et al. 2019; Wang et al. 2022). Furthermore, cordycepin alleviates long-term potentiation (LTP) impairment and protects pyramidal cells in the hippocampal CA1 region against cerebral ischemia and excitotoxicity (Cao et al. 2019). It alleviates dendritic morphology damage and synaptic dysfunction in ischemic models (Chen et al. 2021). Additionally, *Cordyceps* and its components, including cordycepin, have shown potential in protecting against cerebral and myocardial ischemia-reperfusion injury by improving blood perfusion, suppressing inflammation, preventing cellular apoptosis, and promoting tissue regeneration (Li et al. 2024).

Furthermore, cordycepin extract has demonstrated significant neuroprotective effects in traumatic brain injury (TBI) and hypobaric hypoxia models. In TBI mice,

cordycepin administration improved long-term neurological outcomes, preserved white matter integrity, and reduced neuronal tissue loss (Wei et al. 2021). It inhibited pro-inflammatory microglia/macrophage polarization while promoting anti-inflammatory responses. Cordycepin also attenuated blood–brain barrier (BBB) disruption by suppressing MMP-2 and MMP-9 activities and neutrophil infiltration. In hypobaric hypoxia-exposed rats, cordycepin ameliorated cognitive impairment and BBB disruption by inhibiting the TLR4/NF-κB/MMP-9 pathway (Liu et al. 2022a). Mechanistically, cordycepin acts by downregulating adenosine A2 receptor, inhibiting microglial activation, and suppressing neuroinflammatory markers such as NF-κB, NLRP3 inflammasome, and pro-inflammatory cytokines (Govindula et al. 2021).

11.3.2 Mushrooms Enhancing Neurogenesis and Synaptic Plasticity

Neuroplasticity, encompassing synaptic, structural, and functional plasticity, forms the biological basis for learning and memory (Fuchsberger and Paulsen 2022). Synaptic plasticity, the activity-dependent change in neuronal connection strength, is crucial for memory formation and maintenance through processes like Long-Term Potentiation and Depression (Magee and Grienberger 2020; Fuchsberger and Paulsen 2022). Certain medicinal mushrooms, such as Lion's Mane (*H. erinaceus*), have been shown to stimulate NGF and BDNF production, promoting neuronal growth and connectivity. Lion's Mane mushroom has shown promising neuroprotective and neuroregenerative properties. Its bioactive compounds can stimulate the production of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (Deshmukh et al. 2021; Ryu et al. 2021). These compounds promote neurite outgrowth, enhance memory, and support cognitive function (Martínez-Mármol et al. 2020; Ryu et al. 2021). Notably, N-de phenylethyl isohericerin (NDPIH) and *hericene A* have demonstrated BDNF-like activity, improving learning and memory in animal studies (Martínez-Mármol et al. 2020). The mushroom's neuroprotective effects are attributed to its ability to cross the blood–brain barrier and stimulate NGF production (Basko et al. 2023). These properties make Lion's Mane a potential treatment for various neurological disorders, including cognitive decline, dementia, and peripheral nerve damage in both humans and animals (Basko et al. 2023; Deshmukh et al. 2021).

Mitochondrial plasticity plays a crucial role in synaptic function and cognitive processing. Mitochondria adapt to neuronal energy demands by altering their form, function, and position, particularly at synapses where energy consumption is highest (Rossi and Pekkurnaz 2019). *Cordyceps militaris*, a medicinal mushroom, has been shown to enhance mitochondrial function by upregulating Krebs cycle dehydrogenases and electron transport chain complex activities, leading to increased ATP levels in rat brains (Veena et al. 2020). Additionally, cordycepin, a compound derived from *Cordyceps,* modulates metaplasticity in the hippocampal CA1 area through adenosine A1 receptors, potentially explaining its cognitive-enhancing

effects (Mai et al. 2021). These highlight the importance of mitochondrial function in synaptic plasticity and cognitive processes, as well as the potential of *Cordyceps* in supporting these mechanisms.

G. lucidum has shown promising neuroprotective effects against neurodegenerative disorders like Alzheimer's disease particularly triterpenes and aromatic meroterpenoids that exhibit potent antioxidant and neuroprotective activities (Wang et al. 2019). These effects contribute to improved cognitive function and delayed progression of Alzheimer's disease. Studies indicate that *G. lucidum* can ameliorate cognitive impairments by inhibiting β-amyloid formation, reducing inflammation, and modulating gene expression (Luz et al. 2023). Its therapeutic potential against Alzheimer's disease involves multiple mechanisms, including inhibiting tau hyperphosphorylation and regulating signaling pathways (Chen et al. 2024). Also, triterpenes and aromatic meroterpenoids isolated from *G. lucidum* have demonstrated potent antioxidant and neuroprotective effects in vitro, showing potential for preventing neurodegenerative diseases (Wang et al. 2019). These studies suggest that *G. lucidum's* antioxidant properties and neuroprotective effects make it a promising candidate for preventing and treating neuronal damage and cognitive impairment associated with aging and neurodegenerative disorders.

11.4 Aging and Neurodegeneration: The Decline of Cognitive Function

As individuals age, the human brain undergoes numerous structural and biochemical changes closely tied to cognitive decline. These aging-associated brain changes include tissue atrophy, neurotransmitter alterations, and cellular damage accumulation (Lee and Kim 2022). Brain aging affects different regions and cell types variably, with thinning, volume reduction, and iron accumulation observed in specific areas (Chen et al. 2024). Neurons experience reduced dendrites, axons, and synapses, while glial cells often become reactive (Chen et al. 2024). Oxidative stress, cellular senescence, inflammation, and DNA damage contribute to morphological and functional decline, particularly in regions like the prefrontal cortex, hippocampus, and amygdala (Aguilar-Hernández et al. 2023). Understanding these age-related brain changes is crucial for developing interventions to delay or prevent cognitive decline and neurodegenerative diseases.

Reactive oxygen species (ROS) play a crucial role in brain aging and neurodegenerative diseases. While ROS are involved in cellular signaling and metabolism regulation, their overproduction leads to oxidative stress, damaging proteins, lipids, and DNA (Collin 2019). The brain is particularly vulnerable to oxidative damage due to its high oxygen consumption and lipid content (Madireddy and Madireddy 2019). In Alzheimer's disease, ROS production is linked to β-amyloid and tau protein aggregation, creating a self-reinforcing cycle of neurodegeneration (Sharma and Kim 2021). However, recent research suggests that ROS functions extend beyond cellular dysfunction, acting as important second messengers in cell development, proliferation, and survival (Tauffenberger and Magistretti 2021; Bhatia and

Sharma 2021). In addition to oxidative stress, mitochondrial dysfunction emerges as a critical factor in the aging brain. The brain's high energy demand makes it particularly vulnerable to mitochondrial impairment (Trigo et al. 2022). With age, mitochondria produce less ATP and generate more reactive oxygen species, leading to oxidative stress and energy deficits in neurons (Woo et al. 2021). This dysfunction affects mitochondrial biogenesis, dynamics, and membrane permeability, disrupting calcium homeostasis and weakening mitochondrial defense systems (Elfawy and Das 2019). Consequently, these changes contribute to cognitive decline, motor incoordination, and behavioral inconsistencies in aging individuals (Dhote et al. 2021). Mitochondrial dysfunction is implicated in various neurodegenerative disorders, including Alzheimer's, Parkinson's, and Huntington's diseases (Woo et al. 2021; Elfawy and Das 2019).

Chronic neuroinflammation and oxidative stress are key processes in brain aging and neurodegenerative diseases, as the microglia, the brain's immune cells, become hyperactive with age, releasing pro-inflammatory cytokines and contributing to synaptic dysfunction (Triviño and von Bernhardi 2021). This chronic low-grade inflammation, known as inflammaging, leads to microglial priming and impaired clearance capacity (d'Avila 2020). The interaction between neuroinflammation and oxidative stress creates a self-perpetuating cycle that intensifies neurodegenerative changes (Abadin et al. 2024). Recent research highlights the decline of adult hippocampal neurogenesis (AHN) with age and its significant impairment in Alzheimer's disease (AD) (Babcock et al. 2021; Kim et al. 2022). This reduction in neurogenesis contributes to cognitive decline and memory loss associated with aging and AD (Babcock et al. 2021). The vascular system plays a crucial role in supporting neurogenesis by delivering oxygen and nutrients to neural stem cells (NSCs) (Watanabe et al. 2020). However, age-related vascular changes, including atherosclerosis and capillary loss, impair cerebral blood flow and exacerbate neural dysfunction (Watanabe et al. 2020). Additionally, vascular senescence and alterations in blood composition negatively impact NSC potential and contribute to neurogenic decline (Rojas-Vázquez et al. 2021). The accumulation of amyloid β, a key feature of AD, is associated with vascular aging and impaired clearance mechanisms (Watanabe et al. 2020).

Synaptic loss further significantly contributes to cognitive decline in aging and neurodegenerative diseases. Research indicates that tau accumulation in synapses promotes synaptic loss, which can be mitigated by lowering Synaptogyrin-3 (Gratuze and Holtzman 2021). Age-related synaptic dysfunction is driven by calcium dyshomeostasis and alterations in glutamatergic transmission, with adenosine A2A receptors playing a crucial role (Temido-Ferreira et al. 2019). Levels of presynaptic proteins, such as complexin-I and complexin-II, are associated with cognitive variation from normal to dementia (Honer et al. 2019). Furthermore, beyond these intrinsic aging processes, protein misfolding and aggregation are hallmarks of aging and neurodegenerative diseases. Studies show a significant accumulation of misfolded protein aggregates in aged samples across various biological systems (Cuanalo-Contreras et al. 2023). Amyloid-beta (Aβ) and tau proteins, normally present in the body, can become prone to aggregation under pathological conditions,

contributing to diseases like Alzheimer's and Parkinson's (Abyadeh et al. 2024). The aberrant folding of these proteins can induce misfolding in other proteins, supporting the "prion hypothesis" and potentially explaining the progressive nature of neurodegenerative disorders (Lukiw 2022). Protein misfolding disrupts proteostasis, leading to aggregation and neurotoxicity through cellular stress pathways (Gandhi et al. 2019). This process is age-associated and affects specific brain regions, resulting in various neurodegenerative diseases.

11.5 Medicinal Mushrooms as Neuroprotective Agents

Medicinal mushrooms have recently been highlighted in studies as potential neuroprotective agents because of their bioactive compounds that have antioxidant, anti-inflammatory, and mitochondrial supporting properties (Apparoo et al. 2022; Jiang et al. 2024). *Grifola frondosa*, *Lignosus rhinocerotis* and *H. erinaceus* fungi have demonstrated potential to improve cognitive function, reduce neurotoxicity, as well as promote neuronal survival. So these mushrooms may control neuroinflammation, modulate essential biochemical pathways like that of neurotrophin or acetylcholinesterase activity (Rai et al. 2021). These fungi are believed to protect neurons through their bioactive molecules, of which polyphenols, terpenoids, and polysaccharides play a key role in promoting brain health, and thus it is a valuable focus in natural therapy for neurodegenerative diseases.

11.5.1 Antioxidant and Anti-Inflammatory Properties of Medicinal Mushrooms

Medicinal mushrooms, such as *H. erinaceus* (Lion's Mane), *G. lucidu*m (Reishi), and *C. sinensis,* contain powerful antioxidants such as polysaccharides, flavonoids, and phenolic compounds, which scavenge free radicals and prevent oxidative damage (Apparoo et al. 2022; Kou et al. 2021b; Łysakowska et al. 2023). Chronic neuroinflammation, driven by microglial activation and elevated levels of pro-inflammatory cytokines, exacerbates neuronal degeneration (Zhang et al. 2023). Studies have demonstrated that ganoderic acids from Reishi and cordycepin from *Cordyceps* can suppress inflammation by inhibiting nuclear factor-kappa B (NF-κB) signaling pathways and modulating cytokine production (Tan et al. 2021; Sharma et al. 2023; Wang et al. 2024a). These anti-inflammatory properties contribute to maintaining neuronal integrity and preventing cognitive decline.

11.5.2 Role in Neuroprotection and Mitigation of Neurodegenerative Processes

Medicinal mushrooms promote neuroprotection through multiple mechanisms. *H. erinaceus* is particularly notable for its ability to stimulate nerve growth factor

(NGF) synthesis, which enhances neuronal survival, synaptic plasticity, and nerve regeneration (Szućko-Kociuba et al. 2023). Since NGF is essential in maintaining cognitive function, this makes Lion's Mane a promising fungus for preventing and slowing neurodegenerative diseases.

Protein misfolding and aggregation are two key features of neurodegenerative diseases (Koszła and Sołek 2024). Bioactive components in medicinal mushrooms help prevent misfolding and aggregation of these proteins. Beta-glucans and triterpenes found in these fungi exhibit protective effects against amyloid-beta toxicity and tau protein hyperphosphorylation, reducing neuronal apoptosis and synaptic dysfunction (Silva et al. 2023).

Mushroom bioactive compounds, including polysaccharides and terpenoids, have been demonstrated to modulate inflammatory pathways, decreasing chronic neuroinflammation and brain protection from subsequent damage (Rowaiye et al. 2022; Li et al. 2023). Moreover, these fungi have a unique role in modulating acetylcholinesterase activity, and this is pertinent because excessive AChE activity is known to be involved in Alzheimer's disease and, hence, cognitive decline. Medicinal mushrooms help maintain acetylcholine levels by inhibiting acetylcholinesterase, thereby leaving acetylcholine levels balanced and hence, better cognitive function (Sutthibutpong et al. 2024). In addition, some medicinal mushrooms have been reported to stimulate the synthesis of neurotrophins, a class of proteins that promote the growth, survival, and differentiation of neurons. Together, these effects add up to the total neuroprotective potential of mushrooms and offer them prospects as a possible means of limiting the advancement of neurodegenerative diseases (Rai et al. 2021). These properties of medicinal mushrooms make it effective in neuroprotection and retarding neurodegeneration.

11.5.3 Impact on Mitochondrial Function and Energy Metabolism in Aging Neurons

Impaired ATP production, enhanced oxidative stress, and metabolic dysregulation are the major contributors of mitochondrial dysfunction to neurodegeneration (Bustamante-Barrientos et al. 2023). ATP is produced by mitochondria, and when they malfunction, cells may experience energy deficiencies. This is especially harmful for high-energy-demanding cells like neurons, and excess reactive oxygen species (ROS) are frequently produced by dysfunctional mitochondria, causing oxidative stress that damages cellular components and has a role in neurodegenerative disorders.

Medicinal mushrooms are used to support mitochondrial function and enhance energy metabolism (Venturella et al. 2021). *C. sinensis* has been very well known for its capability to enhance mitochondrial biogenesis and ATP synthesis. Molecules such as adenosine and cordycepin prevent aging neurons from metabolic stress and in doing so promote mitochondrial respiration and energy efficiency (Di Lorenzo et al. 2024; Sharma et al. 2023). Similarly, *G. lucidum* has been shown to modulate mitochondrial pathways including sirtuin activation to maintain cellular energy

balance and minimize oxidative stress in studies by Ren et al. (2019) and Xu et al. (2022). These fungi help protect and enhance mitochondrial function, improving mitochondrial pathways and enabling aging neurons to function more effectively. Due to their neuroprotective properties, medicinal mushrooms offer significant benefits for brain health.

11.6 Key Medicinal Mushrooms and Their Effects on Brain Development and Aging

Bioactive compounds found in mushrooms, such as polysaccharides, phenolic compounds, terpenoids, and proteins, protect the neurons, enhance cognition, and promote longevity (Luo et al. 2024). Lion's Mane (*H. erinaceus*), Reishi (*G. lucidum*), *Cordyceps* (*C. sinensis*), Chaga (*Inonotus obliquus*), and Maitake (*G. frondosa*) have drawn attention as a few of the potential species to stimulate nerve growth factor (NGF), reduce oxidative stress, modulate immune responses, and support mitochondrial function—the latter two of which are critical in brain development and maturation as well as for age-related decline (Luo 2024).

11.6.1 Lion's Mane (*Hericium erinaceus*): Neurogenesis and Memory Enhancement

The Lion's Mane mushroom is well known for promoting NGF, an important protein that aids in the survival, growth, and maintenance of neurons (Szućko-Kociuba et al. 2023). According to a study by Docherty et al. (2023), *H. erinaceus* promotes synaptic plasticity, improves memory retention, and promotes neuronal regeneration. The potency of Lion's Mane is due to the presence of hericenones and erinacines, as noted by Lewis et al. (2021). It turns out that it is beneficial for early brain development and neurodegenerative conditions such as Alzheimer's disease (Docherty et al. 2023). It is often combined with Panax ginseng in traditional medicine for effects on memory (Lewis et al. 2021). The results from recent studies have indicated that Lion's Mane extract supplementation increases cognitive function by increasing hippocampal neurogenesis and synaptic connectivity (Chong et al. 2021; Martínez-Mármol et al. 2023). Additionally, human trial studies show memory improvement in humans with mild cognitive impairment after 12–16 weeks of consuming Lion's Mane (Saitsu et al. 2019).

11.6.2 Reishi (*Ganoderma lucidum*): Stress Reduction and Antiaging Effects

Reishi is also known as the "mushroom of immortality" due to its adaptogenic and antiaging properties (Ayesha et al. 2020). More recently, studies have helped confirm these claims and confirmed that Reishi extract had extended lifespan in

Caenorhabditis elegans and promoted autophagy in human cells, which are known to be processes of longevity and health of the cells (Peng et al. 2021). It is a good source of triterpenes and polysaccharides, which regulate the hypothalamic pituitary adrenal (HPA) axis, aiding in reducing chronic stress and inflammation, both of which are factors of accelerated brain aging (Zeng et al. 2021). It also enhances immune function and improves sleep quality, as both are important for neuroprotection and cognitive longevity (Ekiz et al. 2023). Reishi helps slow down age-related neurodegeneration and also improves brain resilience by reducing oxidative stress and promoting mitochondrial function (Ekiz et al. 2023).

11.6.3 *Cordyceps* (*Cordyceps sinensis*): Mitochondrial Support and Cognitive Enhancement

Cordyceps is a unique medicinal fungus known for its ability to enhance mitochondrial energy production, making it beneficial for cognitive endurance and neuroprotection (Yuan et al. 2018). The bioactive compound cordycepin has been shown to improve oxygen utilization, increase ATP production, and protect neurons from oxidative stress-induced damage (Sharma et al. 2023). Sharma et al.'s (2023) research suggests that *Cordyceps* supplementation enhances learning ability and memory retention by reducing neuroinflammation and promoting neuronal survival. These properties make *Cordyceps* a promising natural intervention for developing brains and aging individuals at risk of cognitive decline.

11.6.4 Chaga (*Inonotus obliquus*): Antioxidant Power and Anti-Inflammatory Properties

Chaga mushroom is a potent antioxidant powerhouse, rich in melanin, polyphenols, and betulinic acid, which provide neuroprotection against oxidative stress and inflammation (Ern et al. 2024; Kou et al. 2021b). Chronic oxidative damage has been implicated in both neurodevelopmental disorders and neurodegenerative diseases, making antioxidants like Chaga essential for maintaining brain health across the lifespan (Kou et al. 2021b). A preclinical study by Xin et al. (2021) has demonstrated that chaga extract reduces beta-amyloid accumulation, a key marker of Alzheimer's disease. This can also protect dopaminergic neurons, which are vital in Parkinson's disease. These findings suggest that chaga may have therapeutic potential in preventing and managing age-related cognitive decline.

11.6.5 Maitake (*Grifola frondosa*): Blood Sugar Regulation and Brain Function

Maitake is primarily recognized for its role in blood sugar regulation, which directly impacts brain function and longevity (Wu et al. 2021). Chronic hyperglycemia and

insulin resistance are major risk factors for cognitive impairment, as they contribute to oxidative stress, neuroinflammation, and impaired neurogenesis (Sebastian et al. 2023). A 2020 study also investigated the hypoglycemic and hypolipidemic mechanisms of organic chromium derived from the chelation of Maitake polysaccharides with chromium (III). The study found that this complex improved glucose tolerance and modulated the gut microbiota in diabetic mice, suggesting potential benefits for blood sugar management (Wu et al. 2021). Maitake polysaccharides enhance glucose metabolism and insulin sensitivity, thereby reducing the risk of diabetes-related cognitive decline (Wu et al. 2021). Its immunomodulatory properties help in reducing neuroinflammatory markers, further supporting brain health in both developing and aging populations.

11.7 Mechanisms of Action in Brain Health

Medicinal mushrooms are attracting a lot of interest due to their potential neuroprotective benefits and their ability to enhance cognitive function. Their diverse benefits on brain health can be attributed to several bioactive substances they contain that can affect neurotransmitter balance, modify the gut-brain axis, reduce the levels of oxidative stress and neuroinflammation, and also affect neurotrophic factors (Venturella et al. 2021).

11.7.1 Modulation of Neurotrophic Factors (BDNF, NGF)

Neurotrophic factors, including glial cell-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF), may stimulate the growth and development of neurons and provide them protection from harm and deterioration (Nicoletti et al. 2022). Consequently, substances that have similarities to neurotrophic factors or their stimulants can be used to treat neurodegenerative conditions. As a result of their many biologically active substances, medicinal mushrooms have drawn interest for their possible neuroprotective qualities. *H. erinaceus* (Lion's Mane or Monkey head mushroom) is the most promising of the different medicinal mushrooms available. It contains substances like erinacines and hericenones that can promote the production of nerve growth factor (NGF). For nerve cells to grow, and survive—especially in the hippocampus, the brain's cerebral cortex, and basal forebrain—NGF is essential. These mushrooms have the potential to promote brain plasticity and aid the formation of neurons by increasing the synthesis of NGF (Roda et al. 2021; Szućko-Kociuba et al. 2023).

In a study done by Kou et al. (2022), it was discovered that *I. obliquus,* also known as the chaga mushroom, has protective effects on neurons via stimulating the synthesis of brain-derived neurotrophic factor (BDNF). In this study, a new triterpenoid named 2α-hydroxy-inotodiol (2α-HI, 1) from the chaga mushroom was found to alleviate the effects of oxidative stress and death in nerve cells through the BDNF/

TrkB/ERK/CREB and Nrf2 signaling pathway. This shows that improved survival of neurons and cognitive abilities may be connected to increased BDNF levels.

Yu et al. (2020) in a cohort study observed that elderly individuals who ate medicinal mushrooms for about 2 weeks showed a 50% decrease in the likelihood of experiencing mild cognitive decline as compared with their counterparts who consumed mushrooms no more than once a week. These study results provide credence to the idea that mushrooms and their bioactive compounds can both delay neuronal degeneration and improve cognitive health.

11.7.2 Reduction of Neuroinflammation and Oxidative Stress

Neurodegenerative conditions have been linked to increased oxidative stress and severe neuroinflammation. *H. erinaceus* is antioxidant-rich and also has anti-inflammatory properties, which could minimize damage to neurons. This mushroom contains biologically active substances that can prevent neuronal deterioration and death through inhibiting reactive oxygen species (ROS) and regulating inflammation-related processes (Lew et al. 2020b).

A study reported that feeding mice diets supplemented with *Agaricus bisporus* (White Button Mushroom) can lower levels of oxidative stress in the brain and alter the gut–brain axis. These impacts are linked to changes in the structure of the microbiota of the gut and increased activity of antioxidant enzymes (García-Sanmartín et al. 2022).

11.7.3 Enhancement of Gut–Brain Axis Interactions

The two-way exchange of information between the central nervous system and the gastrointestinal tract is represented by the gut–brain axis. By altering the gut microbiota, medicinal mushrooms can affect this axis. The functions of *H. erinaceus* and *G. lucidum* (Reishi) in gut–brain interactions have been investigated and according to the investigation, these mushrooms can change the composition of the gut flora, which may result in the synthesis of substances that affect mood and functioning of the brain. One of the pathways that regulate this is the CREB/BDNF signaling pathway (Koszła et al. 2025).

11.7.4 Impact on Neurotransmitter Balance and Cognitive Function

The bioactive substances found in medicinal mushrooms have the potential to influence the functioning of neurotransmitters. Serotonin and dopamine are neurotransmitters that are crucial for controlling the mood and cognitive functions, and *H. erinaceus* has been shown to alter their levels. Medicinal mushrooms may help enhance emotional and cognitive health by altering these neurotransmitter pathways (Docherty et al. 2023).

11.8 Medicinal Mushrooms in Diet and Therapeutic Applications

The possible cognitive and neuroprotective benefits associated with incorporating medicinal mushrooms into everyday meals and treatment plans have drawn more attention. Species that are rich in polysaccharides, terpenoids, and phenolic compounds, including *C. militaris*, *G. lucidum*, *H. erinaceus*, and *Lentinula edodes*, have been studied for their potential to modulate brain function and lower the risk of neurodegenerative diseases. The development of functional fungi's pharmacological landscape is influenced by current food habits, supplementation strategies, and clinical findings.

11.8.1 Recommended Dosages and Consumption Methods

Medicinal mushrooms come in a variety of forms, including as powdered substances, extracts, entire dried mushrooms, and supplements in capsule form. The extraction techniques and the quantity of active ingredients determine how effective various forms are.

The neuroprotective properties of *G. lucidum*, a medicinal mushroom containing a wide range of microelements, polysaccharides, triterpenoids, nucleosides, sterols, alkaloids, amino acids, and other pharmacological, bioactive, and nutritionally significant substances, have been investigated; doses vary according to the exact preparation and concentration of active ingredients. Ren et al. (2022) explored the anti-inflammatory effects of *G. lucidum* extract (GLE) on Parkinsonian-like pathological disorder and in their study, 400 mg/kg GLE was administered intragastrically to mouse model of PD with MPTP lesions. Their result showed that GLE altered the concentration of cytokines, prevented microglia activation, as well as reduced abnormal degradation of lysosomes and autophagy.

Similarly, *H. erinaceus*'s cognitive advantages have been investigated in clinical research. In a Placebo-Controlled Study, 3 capsules of *H. erinaceus* mycelia (EAHE), which was about 350 mg/capsule having an active ingredient of 5 mg/g of erinacine was administered daily for 49 weeks to a patient with mild symptoms of Alzheimer's disease and this resulted in notable improvements in cognitive capabilities (Li et al. 2020).

11.8.2 Synergistic Effects with Other Brain-Boosting Nutrients

The cognitive advantages of medicinal mushrooms may be increased when combined with other neuroprotective substances. Polyphenols from sources like blueberries or green tea might improve antioxidant and anti-inflammatory reactions when combined with polysaccharides obtained from mushrooms, improving neuronal health by altering the gut microbiota (Vamanu et al. 2021).

A recent study by Kumar et al. (2025) also proved that the combined administration of extracts from *C. militaris* and Alpha Lipoic Acid (ALA) to aged mice resulted in decreased level of oxidative stress, an increase in antioxidant enzyme activity, and a considerable improvement in cognitive function. This suggests that *C. militaris* and ALA can effectively reduce oxidative stress level and inflammation in the neurons in age-related neurodegenerative disease.

11.8.3 Clinical Studies Supporting Their Effectiveness

Evidence for medicinal mushrooms' ability to improve cognition has come from recent preclinical and clinical research. In addition to the studies on *H. erinaceus* and *G. lucidum* mentioned earlier, another medicinal mushroom known as *C. militaris* has demonstrated neuroprotective properties, possibly by regulating adenosine receptors and reducing oxidative stress. These findings imply that the fungus's anti-inflammatory, antiapoptotic, and antioxidant qualities make it extremely effective at preventing cognitive-related neuronal death in the brain and delaying the onset of memory impairments (Sharma et al. 2023). Kaokaen et al. (2022) observed in a study that the nano-encapsulated extract from *C. militaris* shows promise in ameliorating neuronal diseases both at the genetic and protein levels.

11.9 Future Directions and Recommendations

Research on medicinal mushrooms and their effects on aging and brain development is gaining traction, but some significant gaps remain before their full potential can be realized (Lew et al. 2020a). Large-scale, carefully planned clinical trials that can offer conclusive proof of the neuroprotective qualities of different fungal species in human populations are still lacking, despite an increasing number of preclinical and experimental studies demonstrating these qualities (Badalyan and Rapior 2021; Brandalise et al. 2023). The majority of recent studies use animal and in vitro models, which are instructive but do not necessarily correspond to human neurophysiology (Seyhan 2019; Lancaster 2020). Thus, to confirm the benefits of medicinal mushrooms on cognitive function, neurodegenerative illnesses, and general brain health, future research must give top priority to thorough clinical studies.

The establishment of standardized protocols for clinical trials, including suitable doses, delivery techniques, and long-term effects, is one of the most urgent demands in this sector. There is a dearth of thorough research looking at whole extracts or the synergistic effects of various compounds found in medicinal mushrooms, even though many studies concentrate on isolated bioactive compounds like polysaccharides from *G. lucidum* or erinacines and hericenones from *H. erinaceus* (Chen et al. 2022; Lindequist 2024). The bioavailability and efficacy of these compounds can also be greatly impacted by differences in growing conditions, extraction techniques, and formulation, which calls for standardized approaches to guarantee consistency across studies (López-Hortas et al. 2022). Filling in these research gaps

will help us understand how medicinal mushrooms interact with the human nervous system and whether they can be incorporated as effective therapeutic options.

Medicinal mushrooms provide prospective therapeutic intervention options in light of the rising incidence of neurodegenerative illnesses including Parkinson's and Alzheimer's (Govindarajulu et al. 2021). Numerous species, such as *C. sinensis*, *G. lucidum*, and *H. erinaceus*, have been demonstrated to have neuroprotective effects through the promotion of nerve growth factor (NGF) synthesis, antioxidant activity, and anti-inflammatory qualities (Govindarajulu et al. 2021; Rai et al. 2021; Brandalise et al. 2023). These processes imply that medicinal mushrooms may aid in neuronal regeneration and repair in addition to slowing cognitive decline. However, due to a lack of human investigations, the application of these findings in clinical practice is still restricted (Szućko-Kociuba et al. 2023; Brandalise et al. 2023). To proceed, scientists need to create clinical studies that precisely evaluate how medicinal mushrooms affect the course of the disease, cognitive abilities, and overall quality of life in those suffering from neurodegenerative diseases.

Furthermore, because neurodegenerative illnesses are complicated, a multimodal strategy that takes lifestyle, environmental, and genetic variables into account is necessary. Future studies should examine how medicinal mushrooms may be included in all-encompassing treatment plans, either as stand-alone treatments or as supplements to traditional therapies. Determining their function in contemporary neurology and geriatric care will need examining their long-term effects, possible contraindications, and interactions with pharmaceutical medications (Camilleri et al. 2024). Furthermore, bioactive substances may be optimized to improve their neuroprotective potential and focused therapeutic uses thanks to developments in biotechnology and molecular research (Venturella et al. 2021).

Medicinal mushrooms have great potential for incorporation into brain health and customized dietary plans, in addition to their use in the treatment of neurodegenerative diseases. With its emphasis on individualized treatments based on each patient's unique genetic predispositions, lifestyle choices, and metabolic profiles, personalized medicine is becoming more and more popular. With their wide range of bioactive components, medicinal mushrooms may be included in individualized diet programs to enhance cognitive function and fend against age-related decline (Feng et al. 2019). A noninvasive, preventative strategy for preserving brain health throughout life may be provided by functional foods and nutraceuticals made from medicinal mushrooms (Łysakowska et al. 2023).

Investigating the effects of medicinal mushrooms on the makeup of the microbiome and gut-derived neuroactive substances is especially important given the increased interest in the gut–brain axis and its involvement in cognitive function. Certain species, like *H. erinaceus*, have shown prebiotic qualities, indicating that they may support cognitive health by regulating gut microbiota and systemic inflammation in addition to having direct neuroprotective effects (Priori et al. 2023; Araújo-Rodrigues et al. 2024). Future research should look more closely at these relationships as they may result in new dietary strategies that use the gut–brain link to improve cognition and protect against neurodegeneration (Fekete et al. 2024).

As the world's population ages, it is more important than ever to create long-term, practical solutions for brain health. With their lengthy history in traditional medicine and growing scientific support, medicinal mushrooms present an intriguing research opportunity (Araújo-Rodrigues et al. 2024). However, more thorough, high-quality research is needed before they may be widely used in clinical and nutritional contexts (Brandalise et al. 2023; Łysakowska et al. 2023). To advance this discipline, cooperation among neuroscientists, physicians, dietitians, and mycologists will be crucial. Medicinal mushrooms may soon be a useful part of brain health initiatives, helping to both prevent and treat cognitive decline by filling in present research gaps, carrying out thorough clinical studies, and investigating novel applications (Cha et al. 2024b).

11.10 Conclusion

This study examined the increasing evidence that supports the neuroprotective properties of medicinal mushrooms throughout life, from brain development in early childhood to cognitive preservation in old age. Significant findings reveal that species like *H. erinaceus*, *G. lucidum*, and *C. sinensis* are rich in bioactive compounds, including erinacines, hericenones, triterpenoids, polysaccharides, and cordycepin, which exhibit antioxidant, anti-inflammatory, neurotrophic, and mitochondrial-supporting effects. These compounds enhance neurogenesis, synaptic plasticity, and neuronal survival by influencing critical pathways such as BDNF/TrkB and NGF signaling, alleviating oxidative stress, and managing the gut–brain axis. Notably, *H. erinaceus* has demonstrated promising results in promoting NGF synthesis and enhancing memory, while *G. lucidum* provides stress relief and supports longevity by regulating the HPA axis. Additionally, mushrooms like *Cordyceps* and Chaga are beneficial for mitochondrial function and reducing neuroinflammation, both of which are vital for safeguarding aging neurons.

However, despite encouraging preclinical evidence, clinical data remains scarce, particularly regarding long-term human outcomes, optimal dosages, and bioavailability. Future studies should focus on conducting large-scale, standardized clinical trials to validate these therapeutic advantages and formulate safe, effective protocols for incorporating them into medical and dietary practices. Investigating synergistic effects with other neuroprotective nutrients and personalized medicine strategies is also advisable. Moreover, exploring how these fungi interact with the gut microbiota could shed light on brain–gut health relationships. In light of the growing global concern over neurodegenerative diseases, medicinal mushrooms offer a promising, natural, and holistic approach to enhancing cognitive resilience and neuroprotection.

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